Twenty-second Annual Meeting — Chicago, Illinois
June 7-10, 1956

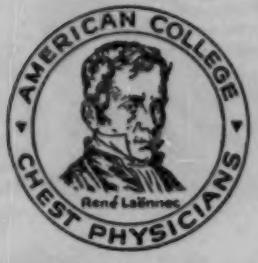
VOLUME XXIX NUMBER 1

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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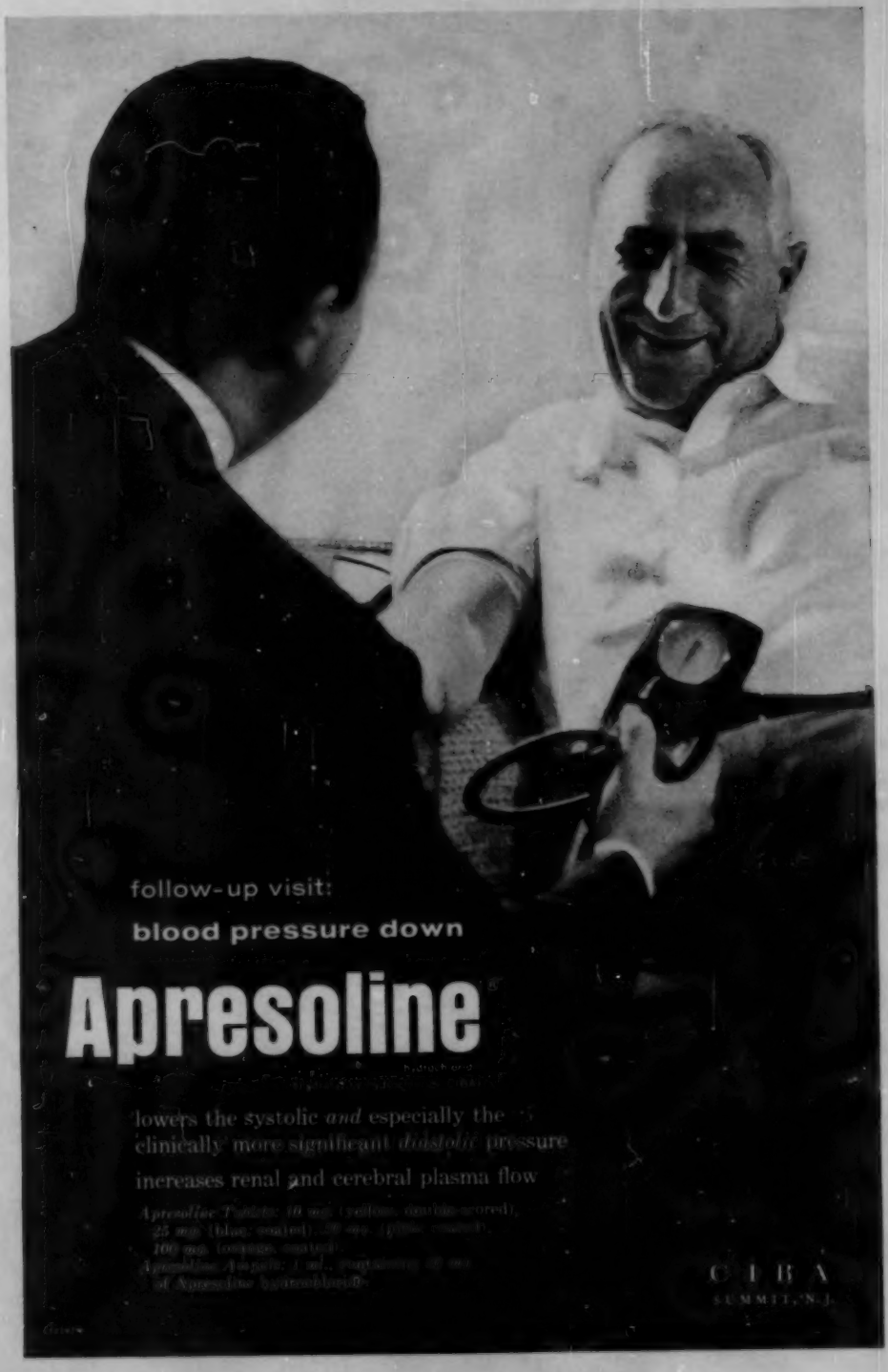

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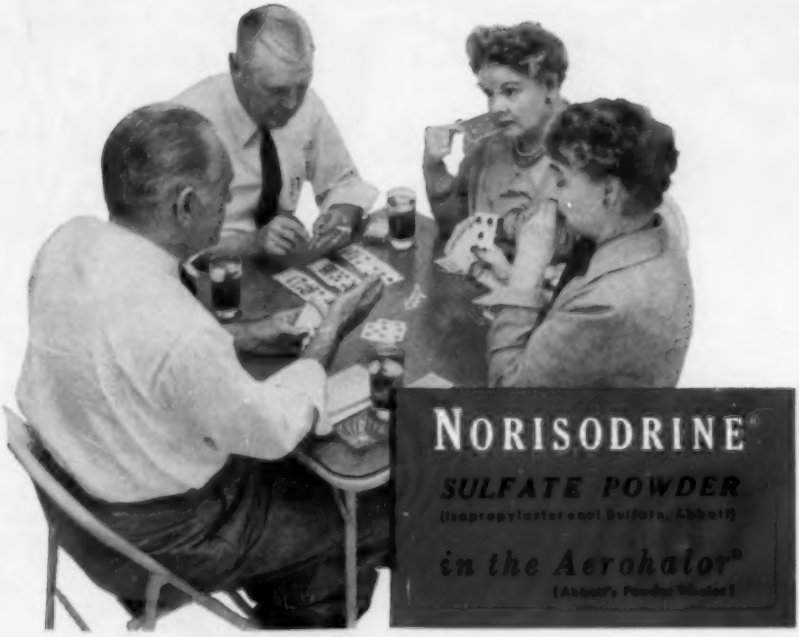

DISEASES *of the* CHEST

OFFICIAL PUBLICATION
OF THE
AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE
112 East Chestnut Street, Chicago 11, Illinois
MURRAY KORNFELD, *Managing Editor*

VOLUME XXIX JANUARY, 1956 NUMBER 1

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1. Hyman, S., and Rosenblum, S. H.: Illinois M. J. 104:257, 1953.
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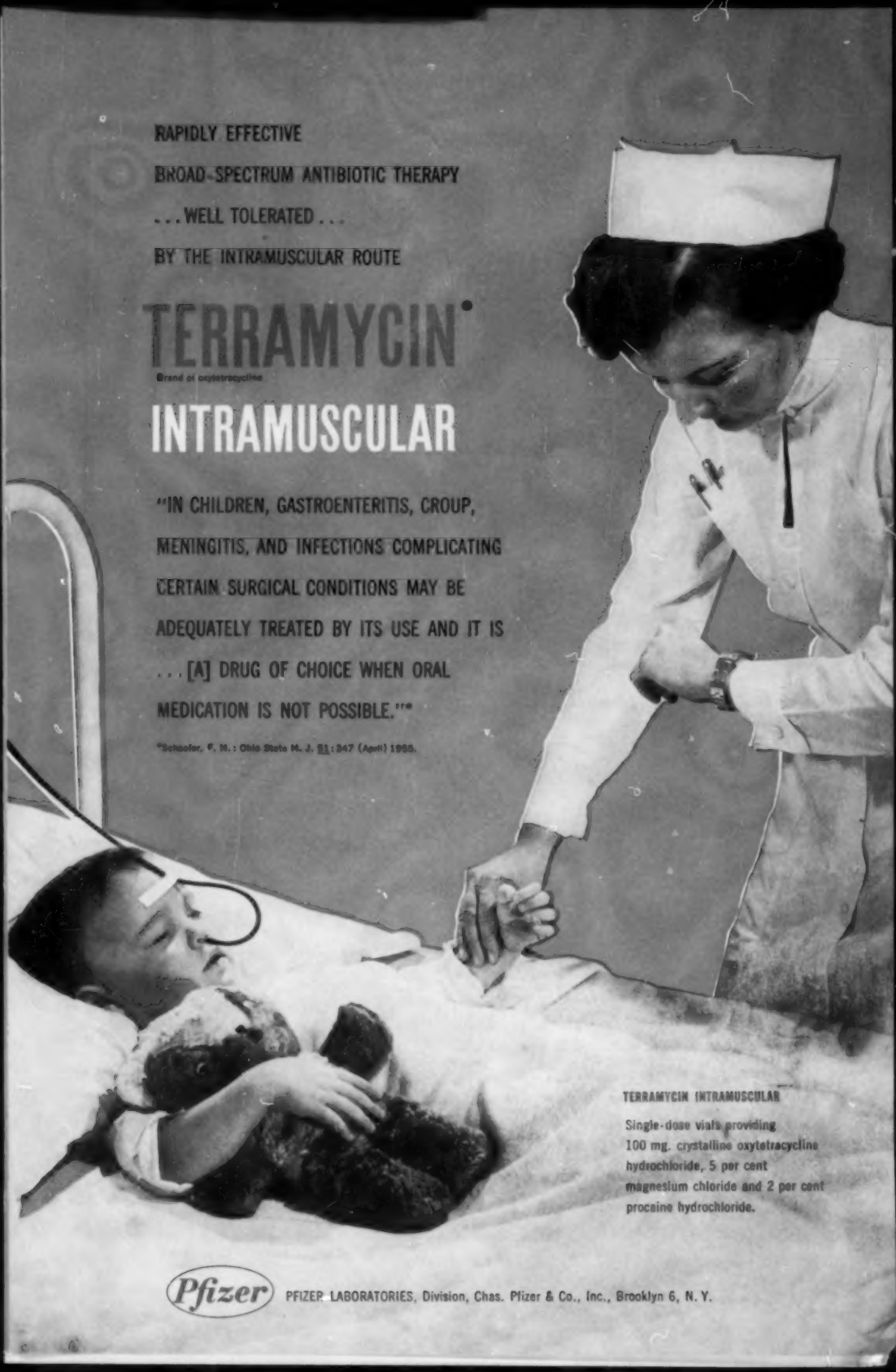
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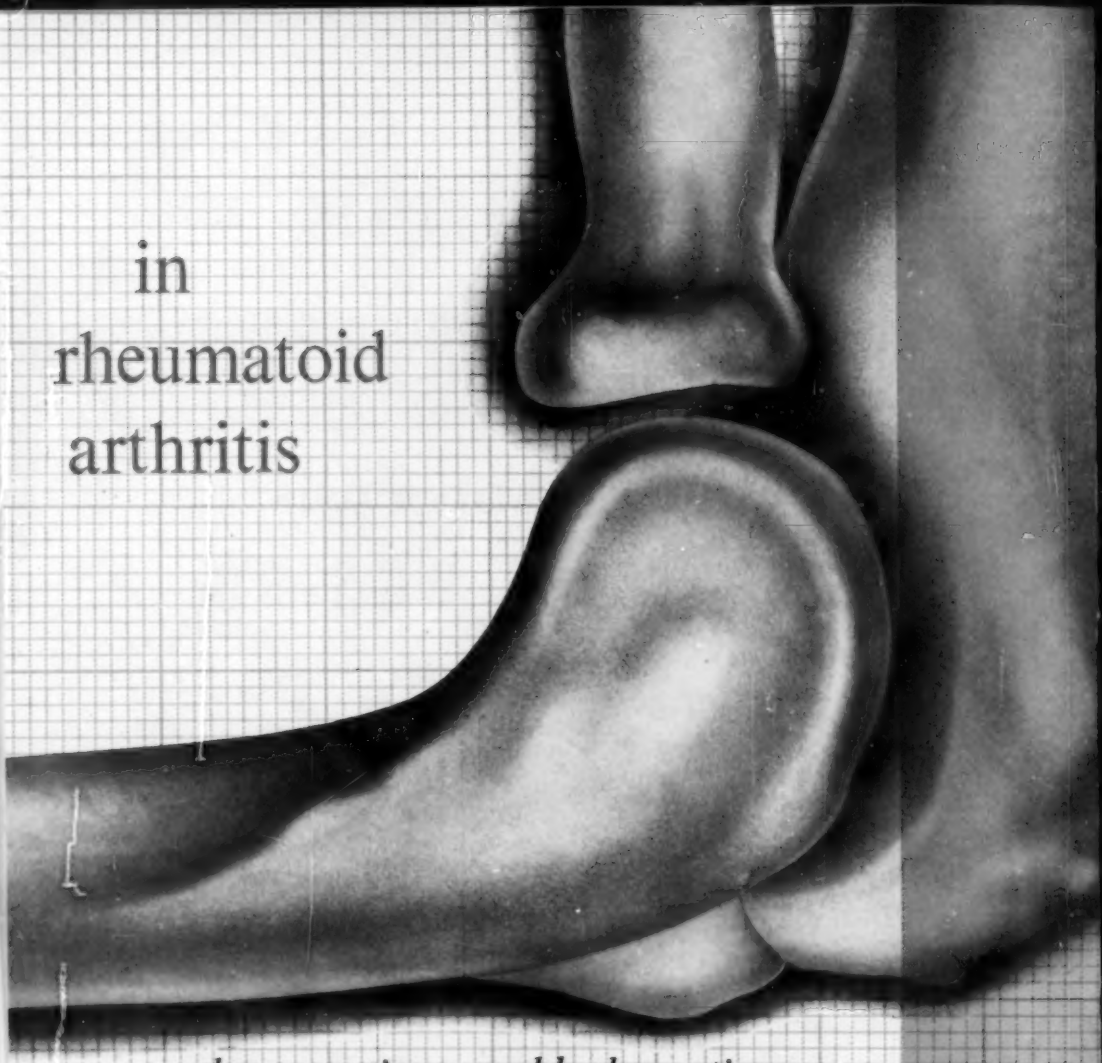

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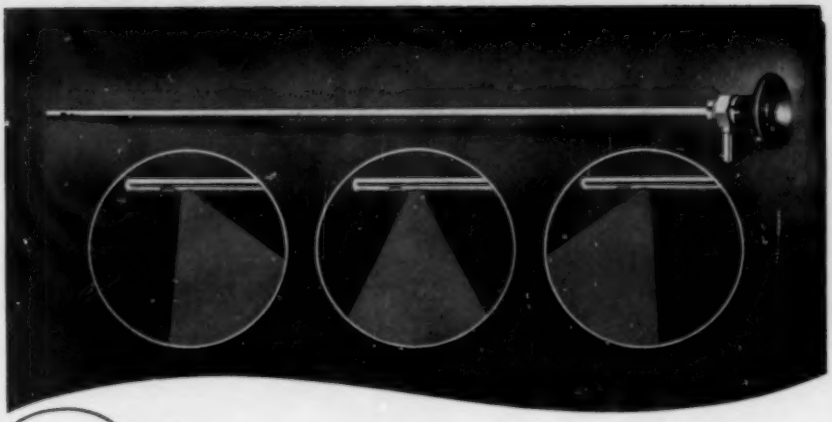

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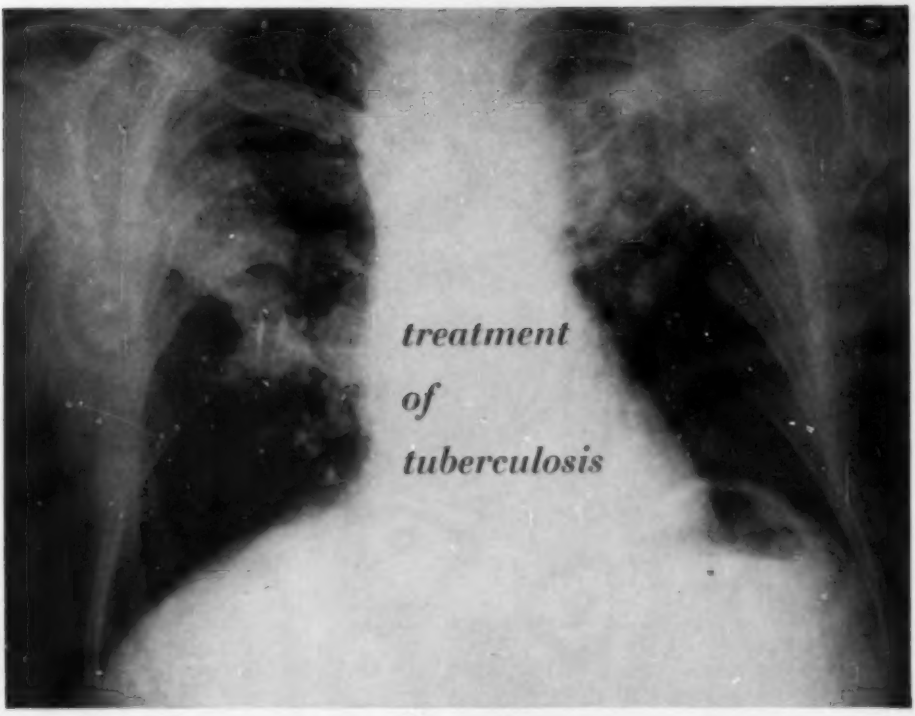

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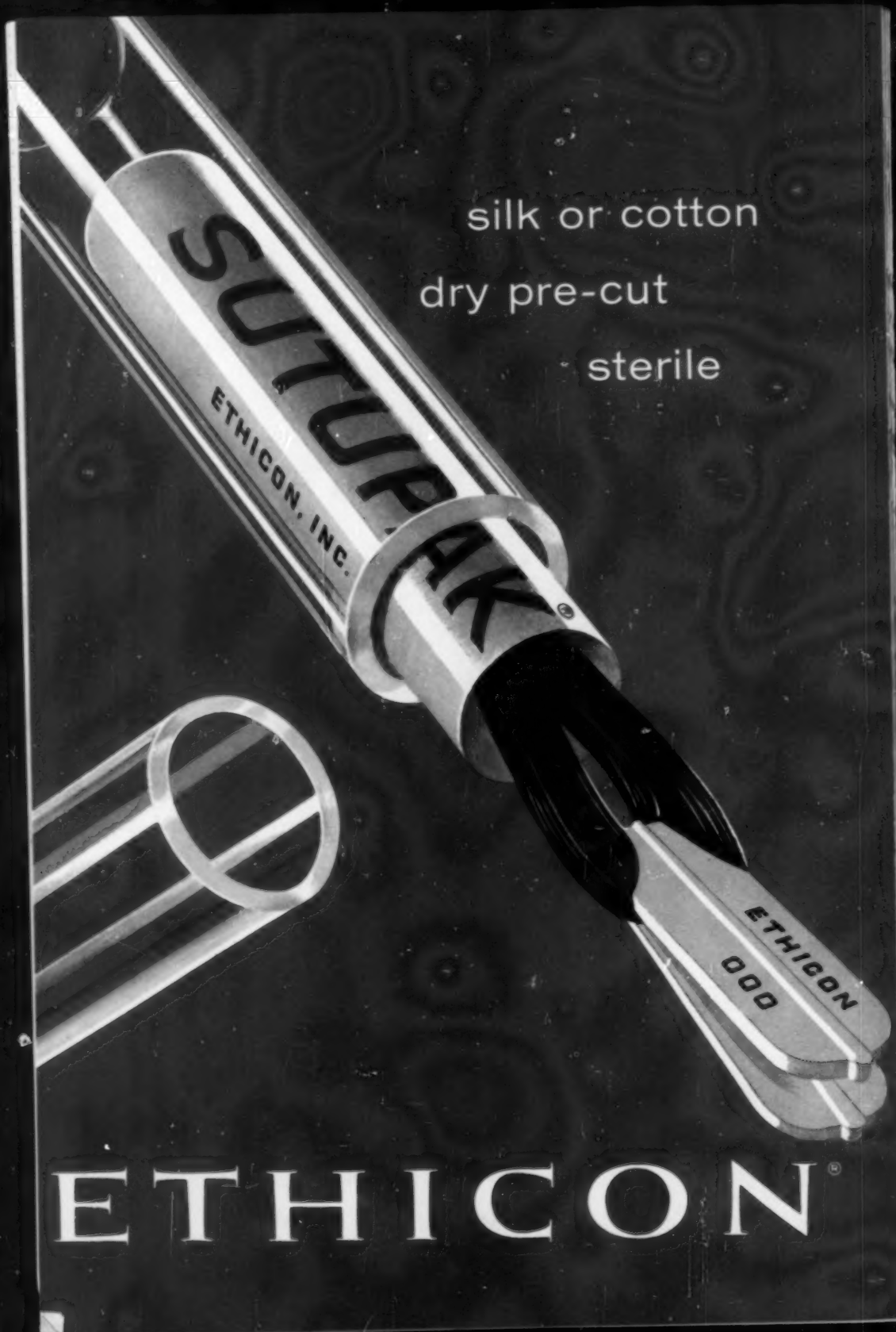
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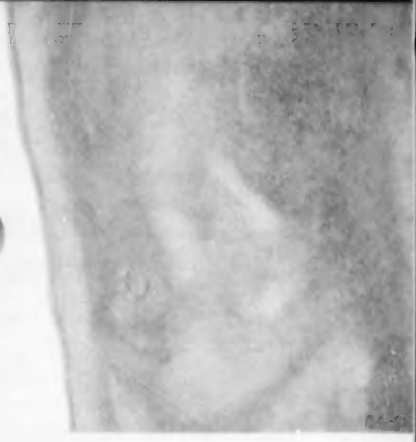

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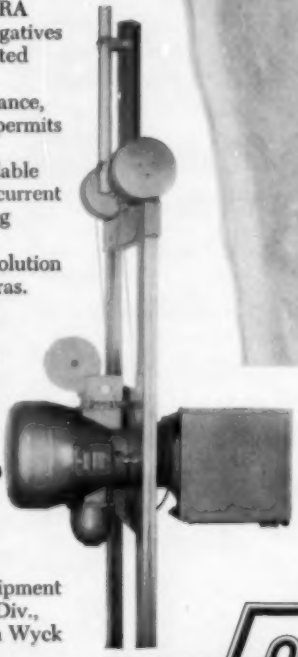

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A Laboratory and Clinical Report on Adrenosem® Salicylate

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History

The first investigation of a hemostat with an action comparable to Adrenosem Salicylate was made by Derouaux and Roskam[1] in 1937. They reported that an oxidation product of adrenalin, adrenochrome (which has no sympathomimetic properties), has prompt hemostatic activity.

It was further found that various combinations of adrenochrome, notably the oxime and semicarbazone, produced stable solutions. But, these were so slightly soluble that sufficient concentration could not be obtained for practical therapeutic use. By combining these adrenochrome compounds in a sodium salicylate complex a stable, soluble form can be obtained. This complex has been given the generic name, carbazochrome salicylate, and is supplied under the trade name Adrenosem Salicylate.

Roskam, in his study entitled "The Arrest of Bleeding,"[2] enumerates "the drugs whose efficaciousness as hemostatics have been proved by accurate methods in experimental animals and in healthy men as well. . . . One is the monosemicarbazone of adrenochrome [Adrenosem Salicylate]."

Chemistry

Adrenosem Salicylate is a synthetic chemical. The full chemical name is adrenochrome monosemicarbazone sodium salicylate complex.

Pharmacology

Although it is chemically related to epinephrine, Adrenosem Salicylate has no sympathomimetic effects. It does not alter blood components, nor does it affect blood pressure or cardiac rate.[2-7]

(* U.S. Patent 2,581,850)

Sherber, in an early study,[3] concludes that Adrenosem Salicylate* "is a potent antihemorrhagic factor in those conditions in which the integrity of the smaller vessels is interrupted, and is superior to any similar material that is now available."

He continues, "From our experience it appears that adrenochromazone complex is indicated in preventing vascular accidents incident to hypertension; in maintaining small vessel integrity; in the preoperative preparation where oozing from a vascular bed is anticipated, as in tonsillectomies, adenoidectomies and prostatectomies; and as an adjunct in the treatment of bleeding from such surgical procedures."

Adrenosem Salicylate may be administered simultaneously (but separately) with any type of anesthetic, anticoagulant, or vitamin K and heparin.

A Unique Systemic Hemostat

Clinical investigators[2-7] are in agreement that Adrenosem Salicylate controls bleeding and oozing by decreasing capillary permeability and by promoting the retraction of severed capillary ends. It aids in maintaining normal capillary integrity by direct action on the intercellular "cement" in capillary walls. The interesting work of Fulton[6] confirms this. Adrenosem Salicylate, since it is not a vasoconstrictor, has no effect on large severed blood vessels and arterioles.

Adrenosem Salicylate is being used both prophylactically and therapeutically in thousands of hospitals, and in virtually every type of surgical procedure. It has also proved most useful in dental surgery.[7]

Owings reported on the use of Adrenosem Salicylate in controlling postoperative adenoid bleeding in 102 cases.[4] "We have used 2½ mg.

(½ ampule) intramuscularly, 15 minutes before anesthesia for children and 5 mg. (1 ampule) for adults." In only one patient did bleeding occur. Three others showed red blood from the nose and mouth. These patients "were then given 5 mg. intramuscularly, with prompt and complete control. We have also noticed that bleeding stopped more promptly on the operating table."

This is a 1% incidence of postoperative bleeding using Adrenosem Salicylate preoperatively, compared to an incidence of 10% postoperative bleeding in all cases taken from previous records, without Adrenosem Salicylate medication.

Peele reports on the use of Adrenosem Salicylate in treating 178 patients with 24 different conditions.[5] The drug was first used to control postoperative hemorrhage from the adenoid region. He adds: "The results were so dramatic that since that date [1953] Adrenosem Salicylate has been used postoperatively to reduce bleeding from all otolaryngologic and bronchoesophagolic procedures, to treat postoperative hemorrhage from the tonsil and adenoid regions, and to treat selected cases of epistaxis."

The effectiveness of Adrenosem Salicylate in controlling bleeding and oozing in 330 patients is reviewed by Bacala.[6] "Our experience of the effect of carbazochrome salicylate on 317 surgical indications and 13 obstetricogynecological conditions, has been therapeutically encouraging and successful for the control of capillary bleeding. Foremost among the cases studied were 223 tonsillectomies definitely benefited by this metabolic hemostat, making a diminution of the control incidence of posttonsillectomy bleeding of 19.8% down to 7%. It has also been found useful in gastro-intestinal bleeding, cataract extraction, epistaxis, incisional seepage, trans-urethral prostatectomy, menometrorrhagias, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and prevention of capillary hemorrhages during hedulin or dicumerol therapy."

Side Effects

All investigators concur that, at recommended dosage levels, Adrenosem Salicylate is free from toxic effects. No cumulative effects attributable to the drug have been reported.

The only side reaction noted has been a transient stinging sensation in the area of injection when Adrenosem Salicylate is used intramuscularly. As one investigator comments: "The brief discomfort which attends the injection of Adrenosem into the gluteal region has not been a significant problem in children or adults as originally anticipated."[6]

Indications

Idiopathic purpura, retinal hemorrhage, familial telangiectasia, epistaxis, hemoptysis, hematuria.

Postoperative bleeding associated with:
tonsillectomy, adenoidectomy and
nasopharynx surgery;
prostatic and bladder surgery;
uterine bleeding;
postpartum hemorrhage;
dental surgery;
chest surgery and chronic pulmonary bleeding.

Dosage

For recommended dosage schedules, please send for detailed literature.

Supplied

Ampuls: 5 mg., 1 cc. (package of 5).
Tablets: 1 mg. S.C. Orange, bottles of 50.
Tablets: 2.5 mg. S.C. Yellow, bottles of 50.
Syrup: 2.5 mg. per 5 cc. (1 tsp.), 4 ounce bottles.

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DISEASES of the CHEST

VOLUME XXIX JANUARY 1956 NUMBER 1

Direct Vision Intracardiac Surgery in Man Using a Simple, Disposable Artificial Oxygenator

C. WALTON LILLEHEI, M.D., RICHARD A. DEWALL, M.D., RAYMOND C. READ, M.D., HERBERT E. WARDEN, M.D. and RICHARD L. VARCO, M.D.

Minneapolis, Minnesota

It has been long recognized that the successful curative treatment of certain congenital malformations and acquired diseases of the heart in man would require an effective method for performing reparative surgery in the open heart under direct vision.

The advent of controlled cross circulation as a successful method for totally by-passing the heart and lungs in man[1, 2] has removed the barrier to intracardiac corrective surgery for many of these congenital defects of the heart heretofore considered inoperable or subjects for palliative procedures only. The malformations which have been successfully corrected by open cardiotomy during the interval while the heart and lungs were totally by-passed using a donor circulation are: ventricular septal defects, atrioventricularis communis, isolated infundibular pulmonic stenosis, tetralogy of Fallot, and pentalogy of Fallot defects.[3, 4]

The ability to carry out definitive reparative procedures inside the human heart under direct vision and at a reasonable risk, promises the early development of curative surgery for other congenital cardiac conditions at present still incurable. Moreover, the scope of expansion both necessary and likely in this field of open heart surgery is impressive. It has been estimated[5] that 50,000 infants are born in the United States each year with congenital heart malformations and since more than one-half of these have components to their defects which will require total by-pass of the heart if they are to be cured, it is evident that a sizable new field of surgical endeavor is in the making. This is not to ignore the additional thousands who have acquired defects of the coronary arteries or cardiac valves of types which are not now curable by existing surgical techniques not involving temporary heart by-pass.

The magnitude of these demands emphasizes the need for techniques widely applicable to the maintenance of the patient's circulation during that interval while his heart and lungs are totally by-passed. The essence

From the Department of Surgery and Variety Club Heart Hospital, University of Minnesota Medical School, Minneapolis, Minnesota.

This research has been supported by the following contributions and grants: (1) Paul Mathieu Fund, (2) Graduate School of the University of Minnesota, (3) Minnesota Heart Association. (4) Life Insurance Medical Research Fund and (5) National Heart Institute, U.S.P.H.S. (Grant No. 830).

of wide applicability is simplicity combined with effectiveness. An important dividend of simplicity is safety. These criteria have received sustained emphasis in our investigative work.

For short intervals, simple mechanical pumps of several types are capable of effectively substituting for this function of the heart. The obstacles to success in this field have been due to the apparent intricacies of developing an efficient arterialization of the venous blood by an artificial or extracorporeal oxygenator which does not irreparably damage the

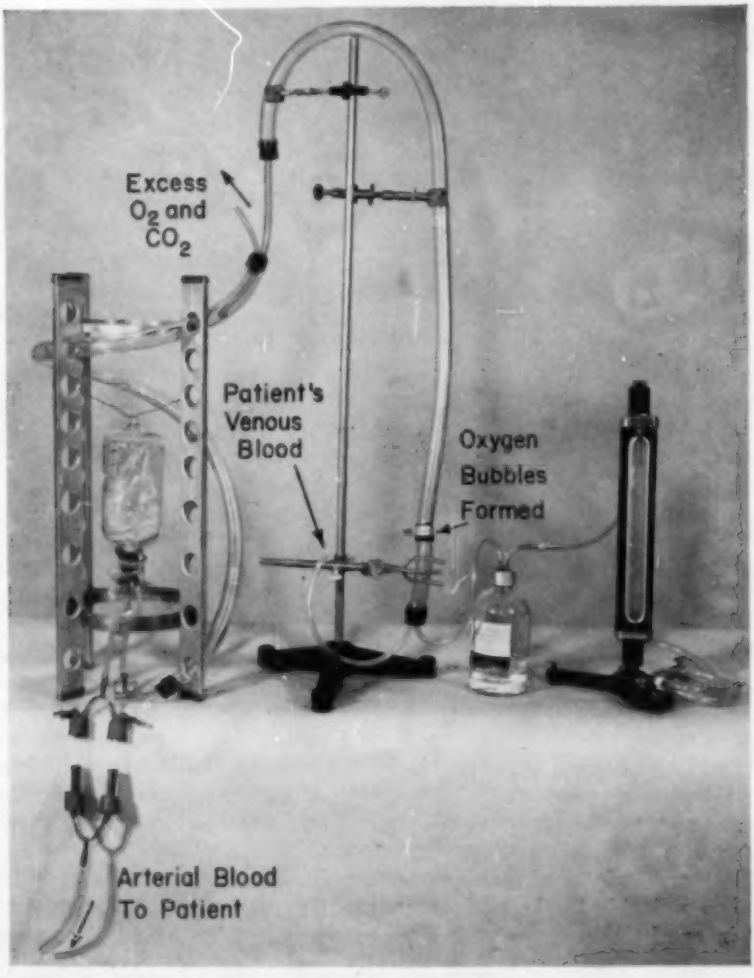

FIGURE 1: The extracorporeal oxygenator utilized for the operative procedures herein reported. From left to right may be noted: the oxygen flow meter (Fisher-Porter), oxygen humidifier, the vertical mixing tube emptying into the spiral settling tube, and the central reservoir from which the blood is perfused through filters to the patient's arterial system.

blood, particularly its clotting mechanisms. The simple oxygenator herein described serves as temporary replacement for the human lungs, and appears to be a significant step forward in the fulfillment of this concept of wide applicability by demonstrating not only the possibility but also the effectiveness of the principle of arterialization of venous blood by the direct introduction of oxygen.

For these operative procedures, this oxygenator was used in combination with the same pump† previously described for use in controlled cross circulation.[3] The low flow principle,[1-4] previously emphasized, has been an important adjunct here also to the successes obtained.

The extensive experimental investigations involved in the development of this oxygenator have been described elsewhere.[7] The oxygenator (Figure 1) has no moving parts, is assembled entirely from commercially available plastic (pure polyvinyl) food hose,* and is sterilized by autoclaving. Because of its simplicity and the fact that the total cost of the component parts is less than five dollars, we have preferred to dispose of it after each clinical case rather than to clean and reuse it. The utilization of plastic is believed important since experimentally it has been found that extensive contact of blood with glass surfaces has deleterious effects upon its clotting mechanisms.

Oxygenation of the venous blood occurs by the direct introduction of 100 per cent oxygen in the form of large bubbles in the vertical plastic tube (mixing tube). The bubbles are obtained by allowing the oxygen to enter the blood near the base of the mixing tube through 18 number 22 standard intravenous needles (with their nub cut off) which have been inserted circumferentially through an ordinary rubber laboratory stopper. The blood-oxygen contact at the surface of these bubbles as they rise in the column of venous blood circulating through the mixing tube presents the large surface area necessary for efficient oxygen uptake and carbon dioxide elimination without the intervention of a foreign substance for filming. The bubbles are then largely dissipated by momentary contact with a potent non-toxic silicone antifoam substance** sprayed or painted on the distal (U shaped) portion of the walls of the mixing tube and the smaller plastic connecting tube.

Any remaining bubbles, because of their relatively large size, rapidly rise to the surface and are eliminated carrying off the carbon dioxide as well as the blood descends by gravity flow in the plastic settling tube (in the form of a helix). From the settling tube the now arterialized blood enters into the central collecting reservoir (an ordinary Kelly flask lined by a polyethylene bag) from which it is perfused through the patient. The oxygenated blood leaving the central reservoir is filtered through standard blood filters.***

During the interval from May 13 to August 9, 1955 there were seven patients, all seriously ill, operated upon by this method for the correction

†Sigmamotor Co., Model T-6S, Middleport, New York.
*Mayon Plastics, Inc., Minneapolis, Minnesota. The plastic tubing used was ¾" I.D. with a ¼" wall.
**Antifoam A, Dow Corning Co., Midland, Michigan.
***Baxter Laboratories, Morton Grove, Illinois, Filter R-19.

of their cardiac septal defects. There have been five successes and two deaths in this series of patients as summarized in Table I. All of the survivors have been discharged from the hospital as normal children cured of their heart defects.

For these operative procedures the patients were heparinized with 1½ mgs. per kilogram of body weight. Heparinized blood (18 mg. heparin mixed with 50 cc. five per cent glucose for each 500 cc. of fresh blood) was used for replacement of the patient's losses during operation. The operative techniques utilized have been described previously.[1-4]

The flow of arterial blood from the pump-oxygenator system during the interval of total heart lung by-pass varied from 172 cc. per minute (D. C.) to 600 cc. per minute (J.N.W.). The patient's plasma hemoglobin levels drawn immediately after perfusion varied from 17 to 45 milligrams per cent.

TABLE I

REPARATIVE SURGERY IN THE OPEN HEART UTILIZING THE SIMPLE, DISPOSABLE ARTIFICIAL OXYGENATOR

Patient	Weight (kg.)	Defect	Direct Vision Intracardiac Procedures	Duration Open Cardiotomy (Min.)	Result
1. J.R. 3 yrs.	9.9	Ventricular septal defect, pulmonary hypertension (70/42), and endocardial fibroelastosis	Ventricular cardiotomy, suture closure of septal defect*	17¼	Died 18 hours postoperatively
2. J.W. 21 mos.	10.5	Tetralogy of Fallot, daily anoxic convulsions	Ventricular cardiotomy, suture closure of septal defect*, resection of infundibular stenosis	18	Living and Well
3. M.D. 2 yrs.	8.0	Atrial septal defect, pulmonary hypertension (75/30)	Atrial cardiotomy, suture closure of septal defect, exploratory ventricular cardiotomy	17½	Living and Well
4. L.B.** 19 mos.	10.0	Ventricular septal defect, pulmonary hypertension (83/54)	Ventricular cardiotomy, suture closure of septal defect	8½	Living and Well
5. D.B. 4 yrs.	13.0	Ventricular septal defect, pulmonary hypertension (78/34)	Ventricular cardiotomy, suture closure of septal defect	13½	Living and Well
6. D.C. 19 mos.	5.3	Ventricular septal defect, pulmonary hypertension (62/35)	Ventricular cardiotomy, suture closure of septal defect*	13¼	Died, 4 days postoperatively
7. J.N.W. 7 yrs.	19.0	Ventricular septal defect, pulmonary hypertension (80/50), cardiac arrhythmia	Ventricular cardiotomy, suture closure of septal defect	12	Living and Well

( ) = The preoperative pulmonary arterial pressures in millimeters mercury.

* Closure stitches tied over a pledget of polyvinyl sponge.

** A plication of the pulmonary artery performed elsewhere at the age of seven months had been unsuccessful in preventing the progression of the pulmonary hypertension.

In patient two the preoperative femoral artery oxygen saturation was 44 per cent. The postoperative value is 92 per cent (Van Slyke analyses).

All seven patients awakened immediately postoperatively, and there was no evidence of neurologic, hepatic, or renal impairment of even a temporary nature. Likewise, there was no abnormal volume of hemorrhage observed in the postoperative interval.

Autopsies were performed in both patients who succumbed, and in each there was a convincing anatomic explanation for the death. At the time of autopsy the ventricular defects were found to be completely and correctly closed in both. Patient 1 (J.R.) had an associated severe endocardial fibroelastosis of the left ventricular muscle, and patient 6 (D.C.) had upon microscopic examination of the lungs widespread and advanced proliferative intimal arteriolar vascular lesions. In neither instance does this cause of death appear to be related in any way to the pump-oxygenator used.

Subsequent and continuing laboratory experiments with higher flow rates have not disclosed any problems concerned with increasing the output of this simple oxygenator sufficiently to supply the needs of adult patients.

Addendum:

To date, a total of 36 patients have had their hearts and lungs totally bypassed for periods of up to 50 minutes utilizing this simple pump-oxygenator system herein described. All of the patients have had a cardiotomy into one or more of their heart chambers for performance of direct vision reparative surgery. These patients have varied in age from 16 weeks to 21 years. Twenty-five patients have had curative surgery for ventricular septal defects associated with pulmonary hypertension with seven deaths. Six patients with the tetralogy of Fallot defects have had corrective surgery with two deaths. The remaining five patients have had direct vision intracardiac corrective surgery for atrial septal defect, atrioventricularis communis, or complete transposition of the great vessels. There has been no late mortality in any of these patients.

The last 19 consecutive intracardiac curative operations, all carried out in seriously ill patients with ventricular septal defects or tetralogy of Fallot, have been performed with only two deaths. This evidence of the efficacy of this simple oxygenator has resulted in its superseding completely the use of the human cross circulation donor for oxygenation which previously had set the standards in our clinic for safety and effectiveness because of its physiologic superbness.

SUMMARY

The successful curative treatment of many congenital malformations and acquired diseases of the heart requires an effective method for performing reparative surgery in the open heart under direct vision. The advent of controlled cross circulation as a successful method for totally by-passing the heart and lungs has demonstrated that intracardiac corrective surgery is both possible and feasible for certain of these congenital defects heretofore considered inoperable. This ability to carry out definitive reparative procedures inside the human heart under direct vision and at a reasonable risk has promised the early development of curative surgery for other congenital cardiac conditions as well as acquired diseases of the valves or coronary arteries which are not now curable by existing surgical techniques. The magnitude of these potential demands emphasizes the need for widely applicable techniques for maintenance of the patient's circulation during the by-pass interval. The essence of wide applicability is simplicity combined with effectiveness. The simple disposable artificial oxygenator herein described serves as a temporary replacement for the

human lungs and appears to be a significant step forward in the fulfillment of these concepts of safety and wide applicability.

This oxygenator has no moving parts, is assembled entirely from commercially available plastic tubing, and is sterilized by autoclaving. Oxygenation of the venous blood occurs by direct introduction of oxygen with coincident elimination of carbon dioxide. Because of its simplicity and the fact that the total cost of the component parts is only a few dollars, we have preferred to dispose of the oxygenator after each clinical use rather than to clean and re-use it.

Seven seriously ill children have had intracardiac corrective operations utilizing this artificial oxygenator in combination with a simple pump for total by-pass of the heart and lungs. There were five successes and two deaths in this series of patients. All of the five survivors have been discharged from the hospital as normal children cured of their heart defects. Their preoperative malformations included ventricular septal defects, tetralogy of Fallot, and atrial septal defect with pulmonary hypertension.

RESUMEN

El tratamiento curativo satisfactorio de muchas malformaciones congénitas del corazón así como de enfermedades adquiridas del mismo, requiére un procedimiento efectivo para realizar la cirugía reparativa en el corazón abierto a la vista directamente.

El advenimiento de la circulación desviada controlada como método que hace posible dejar de lado el corazón y los pulmones ha demostrado que es factible la cirugía correctora intracardiaca para estos defectos hasta ahora considerados inoperables.

Esta posibilidad de la cirugía cardiaca a cielo abierto con un riesgo razonable, promete el pronto desarrollo de la cirugía curativa para otras afecciones cardiacas congénitas así como adquiridas de las válvulas o de las coronarias que no son por ahora curables. La magnitud de estas demandas potenciales destaca la necesidad de técnicas de aplicación amplia para mantener la circulación durante la fase de desviación.

La esencia de la aplicabilidad extensa consiste en la sencillez combinada con efectividad. El oxigenador sencillo aquí descrito sirve para la substitución temporal de los pulmones humanos y parece que es un paso significativo hacia adelante hacia esos requerimientos de seguridad y de eficacia.

Este oxigenador no tiene partes móviles, está hecho enteramente con tubos plásticos comerciales y es esterilizado al autoclave. La oxigenación de la sangre venosa se logra por la introducción directa de oxígeno coincidiendo con la eliminación del anhidrido carbónico. Por su sencillez y por el hecho de que el costo total de las partes componentes es sólo de pocos dólares, hemos preferido descartar el oxigenador después de cada uso en lugar de limpiarlo y volverlo a usar.

Siete niños seriamente enfermos han pasado cirugía intracardiaca correctiva utilizando este oxigenador artificial en combinación con una bomba simple para la desviación circulatoria completa del corazón y de los pul-

mones. Hubo cinco resultados satisfactorios y dos muertes en esta serie. Los cinco supervivientes se han dado de alta en el hospital como normales y curados de sus defectos cardiacos. Las malformaciones preoperatorias incluían defectos septales ventriculares, tetralogía de Fallot, y defectos septales atriales con hipertensión pulmonar.

RESUME

Pour obtenir un traitement curatif satisfaisant dans beaucoup de malformations congénitales et d'affections acquises du coeur, il est nécessaire qu'une méthode efficace permette la chirurgie réparatrice sur le coeur ouvert sous vision directe. La circulation croisée contrôlée permet d'isoler le coeur et le poumon. Ainsi a pu être démontrée la possibilité de la chirurgie intracardiaque curative dans certaines de ces anomalies congénitales auparavant considérées comme inopérables. Cette possibilité de mener à bien des procédés réparateurs à l'intérieur du coeur humain sous vision directe et moyennant un risque raisonnable, a permis le dévollopement précoce d'une chirurgie capable de traiter les autres états cardiaques congénitaux, ainsi que les maladies acquises des valvules ou des artères coronaires, qui n'étaient pas curables avec les techniques connues jusqu'alors. L'empleur de ces possibilités augmentent la nécessité de techniques applicables sur une large échelle qui permettent de maintenir la circulation du malade durant le temps de l'intervention. Les principes d'une telle application sont la simplicité combinée à l'efficacité. Le simple dispositif d'oxygénateur artificiel décrit sert à remplacer temporairement les poumons humains et semble avoir permis un pas décisif dans l'application étendue et sans risque de ces conceptions.

Cet oxygénateur ne comprend aucune partie mobile. Il est assemblé entièrement avec des tubes plastiques que l'on peut trouver dans le commerce, et peut être stérilisé à l'autoclave. L'oxygénation du sang veineux se produit par introduction directe d'oxygène avec élimination simultanée de dioxide de carbone. Etant donné sa simplicité et le fait que le coût total des parties qui le composent n'est que de quelques dollars, les auteurs préfèrent jeter l'oxygénateur après chaque emploi plutôt que de le nettoyer et de le réemployer.

Sept enfants gravement atteints ont subi des opérations correctives intracardiaques grâce à cet appareil en combinaison avec une simple pompe pour permettre l'exclusion totale du coeur et des poumons. Il y eut cinq succès et deux morts dans ce groupe de malades. Tous les survivants sont sortis de l'Hôpital comme des enfants normalement guéris de leurs malformations cardiaques. Il s'agissait de malformations ventriculaires septales, d'une tétralogie de Fallot, d'une malformation septale de l'oreillette avec hypertension pulmonaire.

ZUSAMMENFASSUNG

Die erfolgreiche curative Behandlung vieler angeborener Fehlbildungen und erworbener Krankheiten des Herzens verlangt eine wirksame Methode zur Durchführung reparativer Eingriffe am offenen Herzen unter direkter Sicht. Das Aufkommen eines Kreislaufes überkreuz unter Kontrolle als eines erfolgreichen Verfahrens zur völligen Umgehung von Herz und Lunge hat bewiesen, dass intracardiale korrigierende Eingriffe möglich

und durchführbar sind für bestimmte dieser bisher als inoperabel bezeichneten angeborenen Fehler. Diese Möglichkeit zur Vornahme von endgültigen Wiederherstellungs-Massnahmen im Inneren des menschlichen Herzens unter direkter Sicht und mit verantwortbarem Risiko hat die Erwartung erweckt auf eine frühzeitige Entwicklung von curativen Operationen sowohl bei anderen angeborenen Herzleiden als auch bei erworbenen Klappenfehlern oder Erkrankungen der Coronar-Arterien, die bisher mit den bestehenden chirurgischen Techniken nicht zu heilen waren. Das Ausmass dieser möglichen Anforderungen verdeutlicht die Notwendigkeit eine allgemein anwendbaren Technik, um den Blutkreislauf des Patienten während des Umgehungs-Intervalls aufrecht zu erhalten. Das Wesen einer allgemeinen Anwendbarkeit ist Einfachheit in Verbindung mit Wirksamkeit. Der einfach zu gebrauchende, hier beschriebene künstliche Sauerstoffsättiger dient als zeitweiliger Ersatz für die menschliche Lunge und erscheint als ein bedeutender Schritt vorwärts in der Erfüllung dieser Planungen von Sicherheit und allgemeiner Anwendbarkeit.

Dieser Sauerstoffsättiger hat keine sich bewegenden Teile, ist ganz zusammengesetzt aus im Handel zur Verfügung stehendem plastischen Röhrenmaterial und wird im Autoklaven sterilisiert. Die Sauerstoffsättigung des venösen Blutes erfolgt durch direkte Einführung von Sauerstoff mit gleichzeitiger Ausscheidung von Kohlensäure. Wegen seiner Einfachheit und der Tatsache, dass die gesamten Kosten der Bestandteile nur wenige Dollar betragen, haben wir es vorgezogen, eher den Sauerstoffsättiger nach jeder Benutzung in der Klinik zu vernichten, als ihn zu reinigen und wieder zu benutzen.

7 schwerkranke Kinder wurden mit intracardialen Korrektur-Operationen behandelt unter Benutzung dieses künstlichen Sauerstoffsättigers in Verbindung mit einer einfachen Pumpe zur völligen Umgehung von Herz und Lunge. In dieser Gruppe von Patienten verliefen 5 erfolgreich und 2 endeten tötlich. Alle 5 Überlebenden wurden als normale Kinder aus dem Krankenhaus entlassen mit Heilung ihres Herzleidens. Ihre preoperativen Missbildungen waren Kammerseptum-Defekte, Fallot'sche Tetralogie und Vorhofsseptum-Defekt mit Lungenhochdruck.

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Chest Disease in Patients with Agammaglobulinemia*†

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Introduction

As a new disease entity is studied it becomes apparent that certain clinical and laboratory features are particularly helpful to the clinician in the recognition of the disorder. A consideration of the recent literature indicates that recurrent pulmonary disease has assumed this role in the disease syndrome associated with agammaglobulinemia. Recurrent pulmonary infections including bronchitis, pneumonitis, and pneumonia at times leading to pulmonary fibrosis, bronchiectasis, and empyema, appear to be extremely frequent manifestations of agammaglobulinemia and as reporting becomes more complete it seems likely that pulmonary disease may become the clinical *sin qua non* of this syndrome. Consequently, it seems especially pertinent that a complete review of reported cases of agammaglobulinemia be submitted to chest physicians who are among those most likely to encounter patients suffering from this metabolic disturbance. It is the purpose of this report to present a thorough review of the reported experience with agammaglobulinemia and to emphasize the pulmonary manifestations observed in our cases and those studied by others.

Agammaglobulinemia is a metabolic disorder featured by an enhanced susceptibility to bacterial infection, absence of gamma globulin from the serum, absence of antibodies from the blood and tissues, and failure of immunologic response to antigenic stimulation.[1-3] Evidence has been submitted indicating that this disorder reflects a disturbance in function of the hematopoietic reticulum (mesenchyme) which is expressed in each patient as a failure of plasma cell formation and consequent failure of antibody production in response to antigenic stimulation.[4-8]

On the basis of clinical and laboratory data this disorder can be subdivided into a congenital and an acquired type.[3, 8] In both diseases the chief clinical manifestation is the occurrence of recurrent severe bacterial infections. The congenital disease is, in general, expressed early in life, and, like hemophilia, appears to be an inborn error of protein synthesis transmitted as a sex-linked recessive trait.[2, 9] Thus, this form of agammaglobulinemia occurs only in male children, frequently in more than one member of a

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sibship, and suggestive evidence links its transmission to the female. In contradistinction, the acquired diseased is much less selective in nature appearing in either sex at any age. Significantly patients with this form of agammaglobulinemia give a history of having been healthy up to a certain time in their lives. Following what is interpreted to be the development of agammaglobulinemia, changes of a dramatic nature occur, and existence for these people becomes almost a continuous round of bacterial infections. Thus, by history at least, the agammaglobulinemia in these patients has a well defined onset.[3, 9, 10] So far direct biochemical proof of the acquisition of agammaglobulinemia is lacking.

Although the term agammaglobulinemia is used to describe both the congenital and acquired disease, in the strict sense it is probably always a misnomer based on lack of sensitivity of most methods currently used to detect and measure the gamma globulin concentration in the serum or plasma. Critical immunological methods suggest that minute amounts of gamma globulin are present in the serum of almost all of the so called agammaglobulinemic patients.[5, 9, 11] Although there appears to be some overlapping somewhat larger amounts of gamma globulin are generally present in the sera of the patients with acquired agammaglobulinemia than in the sera of those with the congenital disorder.[11] In spite of the obvious differences in the basis of the two forms of agammaglobulinemia a common denominator exists. In both disorders there appears to be a dysfunction of the reticular tissues (mesenchyme) associated with failure of plasma cell and antibody production.[9] Administration of sufficient gamma globulin to bring the serum level to normal does not render either group of patients capable of antibody production.[12]

That Bruton's[1] first description of agammaglobulinemia in 1952 alerted the medical profession to the existence of this disease is attested to by the almost logarithmic increase in case reports appearing in medical journals and at medical and scientific meetings, during the last years.[2, 3, 9, 13-29] In both its forms agammaglobulinemia has now been discovered in numerous clinics in both America and Europe and it seems to conclude that agammaglobulinemia is a widely distributed disease which may be much more common than was anticipated when it was first described. Observations also seem to establish that this disease, as a clinical entity, has been created by antibiotic treatment in our era. Prior to the availability of antibiotics to cure many severe bacterial infections which these patients have, all of them doubtless died early and the clinical syndrome featured by recurrent severe bacterial infection was not expressed. Thus to Bruton goes credit for discovering a new disease which seems to be the product of medical progress. Following Bruton's initial description of the entity, Bruton et al[30] reported two additional patients having agammaglobulinemia, thus launching a nation-wide search for patients with this disorder. These initial cases of congenital agammaglobulinemia lacked immune bodies in their blood and tissues and failed to form antibody in response to stimulation with several bacterial antigens. In 1953 Janeway et al[2] presented clinical and laboratory observations on nine such cases entirely similar to

those of Bruton. All nine cases were males, each suffering from recurrent bacterial infections and failing in their immune response. In spite of the frequency and severity of bacterial infections in these patients it was noted that certain virus diseases gained the usual expression, and lasted the usual lengths of time with recovery occurring in the same way it does in normal persons.

Furthermore, it was noticed that in spite of heavy exposure, recurrence of certain virus infections did not take place. The authors submitted the concept that the agammaglobulinemia occurring in children is an inborn error of metabolism transmitted as a sex-linked recessive trait. Chief among the recurrent infections in these children were pneumonia and meningitis. Subsequently Good[3, 9] and Hayles et al[17] have described an additional nine cases of the congenital disease. Like those cases previously reported, the clinical manifestations in these patients included numerous episodes of bacterial disease ranging from severe diarrhea, recurrent urinary tract and skin infections, to numerous episodes of respiratory infection. Most notable among the infections, however, was the recurrent involvement of the pulmonary parenchyma. In the three cases reported by Hayles et al,[17] each had one severe respiratory infection after another, two of them ultimately dying with respiratory complications. Our six cases of congenital agammaglobulinemia likewise were featured clinically by recurrent pneumonia, one of the patients developing bronchiectasis following several such episodes. Jean[21] reported a case of agammaglobulinemia in a seven year old boy. This child's disease too was featured by recurrent severe pulmonary infections leading to the development of bronchiectasis. That all 24 of the cases of congenital agammaglobulinemia thus far described have occurred in boys supports the concept originally expressed by Janeway et al[3] that congenital agammaglobulinemia is an inborn error of metabolism transmitted as a sex-linked recessive trait.

Hypogammaglobulinemia and even agammaglobulinemia diagnosed according to electrophoretic criteria may occur in other diseases during childhood. For example, in the nephrotic syndrome loss of serum proteins in the urine results in both hypoalbuminemia and hypogammaglobulinemia.[31] Loss of protein and poor nutrition may also result in serum deficiency of globulin as well as albumin in certain cases.[32] As early as 1932 prior to the availability of electrophoretic methods, McQuarrie and colleagues[33, 34] described a patient having generalized edema, low serum proteins and enhanced susceptibility to infection. This patient ultimately died with bronchopneumonia. Fractionation of the serum proteins revealed both a hypoalbuminemia and extreme hypoglobulinemia, the globulin being only 0.4 gram on one occasion. From this protein partition there can be little doubt that the gamma globulin content as well as the content of other serum proteins was low. Cases similar to that described by McQuarrie have been reported by Meyers et al,[35, 36] Schick and Greenbaum[37] and Fried and Henly.[38] Although infection is not a regular concomitant of the latter syndrome, McQuarrie's case indicates that in this disorder, as in isolated agammaglobulinemia, the gamma globulin levels can become so low as to

be associated with failure of the immunological mechanism and increased susceptibility to bacterial disease. It should be emphasized that the syndrome originally described by McQuarrie et al[33, 39] appears to be distinct from the disease described by Bruton. In McQuarrie's syndrome a generalized deficiency in protein fabrication is characterized while in congenital agammaglobulinemia, the failure of gamma globulin formation is an isolated defect.[2, 3, 9] Furthermore, McQuarrie's syndrome may occur in either sex[33, 36, 37, 38] while congenital agammaglobulinemia occurs only in boys.

Hypogammaglobulinemia sometimes of extreme degree may also be noticed when a delayed assumption of gamma globulin synthesis occurs in the newborn period.[40, 41] Although not yet proved it has been suggested that this form of hypogammaglobulinemia too may result in enhanced susceptibility to infection.[42] Indeed preliminary data link the occurrence of certain crib deaths associated with pulmonary disease to this defect in protein synthesis.[42]

As a probable example of transient hypogammaglobulinemia of infancy is the case reported by Keiden et al.[43] The eight week old female infant which they described developed a progressive necrotizing reaction following smallpox vaccination and died with staphylococcus sepsis and bronchopneumonia. Although electrophoretic analysis revealed gamma globulin to be absent from the serum it seems likely that in this child the authors were dealing with a pathological extension of the physiological hypogammaglobulinemia of infancy and that this patient is not an example of isolated congenital agammaglobulinemia occurring in a female. A notable difference between Keiden's case and those studied by Janeway et al[2] and Good et al[3] was the presence of many plasma cells in the inflammatory exudates in Keiden's patient. These cells were virtually absent from the hematopoietic tissues and inflammatory exudates of the cases reported by Janeway and Good. Similar cases of transient hypogammaglobulinemia of infancy have been studied by Kelley et al[44] and Ulstrom et al.[45] In each of the latter two instances electrophoretically determined agammaglobulinemia was associated with increased susceptibility to infection and in each patient the extreme hypogammaglobulinemia was transient. The latter syndrome may occur in either sex and exists in patients two to six months of age following decay of the passively transferred maternal gamma globulin. Agammaglobulinemia in childhood may be based on still another mechanism, namely an increased rate of destruction of normally formed serum protein.[46]

In addition to and apparently distinct from congenital agammaglobulinemia is the acquired disease which occurs primarily in adults and appears to show no preference for age or sex. This disorder like the childhood disease has been expressed clinically by the occurrence of repeated episodes of bacterial infection especially involving the upper and lower respiratory passages. Almost all of these patients have been troubled by recurrent pneumonia and many have developed empyema, pulmonary fibrosis, bronchiectasis or atelectasis. The complete case reports of acquired agamma-

globulinemia present in the literature show that the disease has a wide range with respect to age. The youngest patient was a 17 year old female and the oldest was our 58 year old man. Unlike the congenital disease, there seems to be no sex preference among patients with acquired agammaglobulinemia. In cases reported to date, seven have been females and 12 have been males. Both the younger patients and the older ones suffered from recurrent bacterial pneumonia, and bronchiectasis occurred as a complication in four of the reported cases. Although bronchiectasis has been noted to occur frequently in acquired agammaglobulinemia, the bronchiectasis-agammaglobulinemia syndrome is not distinctive of this form of the disease since four instances of bronchiectasis have also been noted in children having the congenital disease.

As is illustrated by the cases described by Collins and Dudley[25] bronchiectasis may be an early expression of the adult disease. In their patients the most prominent and earliest clinical manifestations of agammaglobulinemia were related to the bronchiectasis. Both of their patients had generalized bronchiectasis and empyema. One case was a 25 year old housewife who expired despite bilateral surgical resection of the involved pulmonary tissue while the other case was a 53 year old woman who expired from pulmonary failure even though surgery was not performed. These two cases emphasize the difficulty of diagnosing agammaglobulinemia unless the responsible physician is aware of its clinical nature. In general, repeated episodes of pneumonia serve to alert the physician to the possibility that agammaglobulinemia exists. In many such patients a fantastic experience with recurrent pneumonia is reported as in the patient reported by Prasad and Kosa[13] who was also studied by Good.[3, 9] This woman suffered at least 34 attacks of pneumonia over an eight year period. In other cases only a few episodes of pneumonia result in irreversible destruction of the pulmonary parenchyma. Bronchiectasis, atelectasis, pulmonary fibrosis or empyema represent the major expression of the pulmonary disease in some of these cases. Following the many attacks of pneumonia, residual fibrosis of the lungs developed in some of these patients. Examples are the 37 year old man studied by Zinneman et al and the 30 year old female studied by Prasad and Kosa and Good.

Although it is clear that agammaglobulinemia occurring in adults is regularly an acquired disease, the literature and studies thus far available do not indicate whether it is a homogeneous entity or whether the failure of gamma globulin and antibody production has had multiple bases expressing themselves in this common metabolic disorder. Pertinent to this consideration is a patient reported by Rundles, Arends and Coonrad[28] in whom a malignant lymphoma apparently resulted in failure of gamma globulin formation and the development of acquired agammaglobulinemia. This patient with a well defined malignant disease of the reticular tissues showed the same symptoms and signs as were noted in the other patients whose agammaglobulinemia was associated with poorly defined disturbance of mesenchymal tissue[3, 8] or in whom no hematological abnormalities were described. In some patients with multiple myeloma who are producing

TABLE I

Pulmonary Manifestations in Patients with Congenital Agammaglobulinemia

Author	Year	No. Patients	Sex	Age	Pneumonia No. Episodes-Type	Pulmonary Complications	Bacteriology	Remarks
Bruton	1952	1	M	8	12 episodes Lobar pneumonia Bronchopneumonia	None	Pneumococcus	Many other kinds of severe bacterial infections
Bruton, et al	1952	2	M	9	Numerous attacks Pneumonia	None	Staphylococcus Pneumococcus	Many other kinds of severe bacterial infections
			M	9	Numerous attacks Pneumonia	None	Hemophilus	Many other kinds of severe bacterial infections
Janeway, et al	1953	all 9 males	M	all children	All cases have had repeated episodes of bronchitis and pneumonia	2 cases bronchiectasis emphysema atelectasis	"Common bacterial pathogens"	Many other kinds of severe bacterial infections
Jean, R.	1953	1	M	7	"Repeated severe pulmonary infections" Pneumonia	Bronchiectasis	Not reported	
			M	7 yr.	8 episodes Lobar pneumonia Bronchopneumonia	None	Pneumococci	Repeated attacks meningitis otitis, diarrhea, pharyngitis
			M	6 yr.	12 episodes Lobar pneumonia Bronchopneumonia	Bronchiectasis Atelectasis	Group A streptococci Pneumococci Staphylococci	Repeated attacks meningitis otitis, diarrhea, pharyngitis

Good, R.	1954	6	M	20 mo.	10 episodes bronchial pneumonia, interstitial pneumonitis	Interstitial Organized	Hemophilus Group A streptococci	Repeated attacks otitis, sinusitis, urinary tract infection
			M	15 mo.	About 10 episodes Bronchial pneumonia, Interstitial pneumonitis	None	Streptococci Staphylococci	Repeated attacks otitis, sinusitis, urinary tract infection
			M	10 yr.	3 attacks Bronchial pneumonia		None	
			M	1 yr.	1 episode Bronchial pneumonia	None	Hemophilus Type B	No other infections
			M	5 mo.	Recurrent attacks bronchopneumonia	Chronic suppurative pneumonitis	Micrococcus pyrogens (staphylococci)	Granulomatous lesions in the liver
Hayles, et al	1954	3	M	9 yr.	Bronchitis Pleuritis	None	Not reported	Recurrent infections meningitis, died with myocarditis
			M	9 yr.	Recurrent pneumonia	None	Not reported	Meningitis, osteomyelitis, virus infections without trouble, pyoderma
Tanis	1955	1	M	2 yr.	Recurrent pneumonia Suppurative bronchitis	None	Proteus	
Fischer	1955	1	M	5 yr.	Recurrent pneumonia and recurrent bacterial respiratory bronchitis infections	None	Not reported	Skin infections, septic arthritis

TABLE II

Pulmonary Manifestations of Acquired Agammaglobulinemia

Author	Year	No. Patients	Sex	Age	Pneumonia No. Episodes-Type	Pulmonary Complications	Bacteriology	Remarks
Young, et al	1954	4	M		Not completely reported			Cases as yet incompletely reported
Prasad & Kosa* Good, R. A.	1954	1	F	30	34 attacks Bronchopneumonia Lobar pneumonia Interstitial pneumonia	Pulmonary fibrosis	Pneumococcus repeatedly	Disease clearly acquired at about 22 years of age. Hypertension
Good, R. A.	1954	1	M	58	17 attacks lobar pneumonia Bronchopneumonia Interstitial	None	Pneumococcus Staphylococcus	Disease acquired 4 years prior to study. Had huge thymoma
Zinneman, et al	1954	2	M	29	Recurrent pneumonia	Bronchiectasis RLL, RML, LLL	Pneumococcus	Began in adult life.
			M	37	1 episode definite bronchopneumonia	Fibrosis basilar lungs	Pneumococcus	Began in adult life.
Grant & Wallace	1954	1	F	17	7 attacks pneumonia	None	Not described	Apparent onset at 15 years,associated Leukopenia
Arends, et al	1954	1	F	53	Repeated, severe respiratory infections	None	Not described	——
Stanford, et al	1954	1	F	39	Bronchitis lobar pneumonia bronchopneumonia	Bronchiectasis both lower lobes	Streptococcus B hemolytic hemophilus influenza	Transient spru-like syndrome. Recurrent parotitis

Rohn, et al	1954	1	M	29	Not completely reported			Hypersplenism corrected by splenectomy
Saslaw, et al	1954	2	M	26	Repeated attacks of pneumonia	None	Bacterial Not further described	——
			M	40	Not completely reported			Repeated infections with a spru-like syndrome
Lange, et al	1954	1	F	29	Numerous lobar episodes, bronchopneumonia	Empyema	None stated	——
Moenke	1954	1	M	18	5 episodes interstitial pneumonia 3 attacks bronchopneumonia	None	Pneumococcus	——
Collins & Dudley	1955	2	F	31	Repeated attacks Bronchopneumonia Lobar pneumonia	Bronchiectasis Empyema	Staphylococcus Coliform org.	Clearly acquired when approximately 24 years of age
			F	57	Repeated attacks Bronchopneumonia Lobar pneumonia	Bronchiectasis Empyema	None stated	Apparently acquired at about 50 years of age
Seltzer, Baron & Taporek	1955	1	M	27	Pneumonia together with pulmonary histoplasmosis	Pulmonary calcification	Histoplasma capsulatum	——

*Same case, L. L., studied by Good & Zinneman and Hall not duplicated in this table.

large quantities of aberrant globulin, immunological capacity may be deficient and virtually no normal gamma globulin is produced.[47-50]

Observations

Summarized in Table I are the pulmonary disturbances thus far reported in children with agammaglobulinemia. Data are included from all the cases presented in the literature as well as our own patients. As may be seen from the Table, wherever reporting has been complete, all of the children suffering from agammaglobulinemia have been troubled with recurrent pulmonary disease including recurrent attacks of pneumonia. In several instances bronchiectasis has been the result of the recurrent pulmonary infection. In many instances the case reports clearly indicated that it was the pulmonary disease which brought the patients to the attention of the medical clinics where the diagnosis of agammaglobulinemia could be made. Wherever bacteriological data was available it was found that the ordinary pyogenic pathogens were the organisms responsible for the recurrent infections. As may be seen in the Table, the organisms most commonly infecting these patients have been the pneumococcus streptococcus, staphylococcus and hemophilus. Summarized in Table II are the cases of acquired agammaglobulinemia reported to date. It may readily be seen from the Table that in this syndrome, among the most prominent manifestations are pulmonary disorders. Severe life-threatening pulmonary complications include bronchiectasis observed on four occasions, and empyema observed in three cases. In addition late pulmonary fibrosis was described in two instances and generalized calcification due to histoplasmosis in one. In these patients as in the children the organisms producing infections have been primarily the usual pyogenic pathogens. The pneumococcus has been particularly troublesome, for example, producing in one of our cases many attacks of pneumonia and at least four attacks of meningitis.

In Table III the observations detailed in Tables I and II are digested and summarized. Although the opinion has been expressed that patients with acquired agammaglobulinemia have bronchiectasis more frequently than do patients with the congenital disease, the reported experience does not give full support to this view. Four of the 24 patients with congenital agammaglobulinemia have been shown to have bronchiectasis whereas four of 13 completely reported patients with the acquired disorder have developed this complication. Thus, to date it appears that of the pulmonary complications, noted in cases with recurrent pneumonitis, bronchiectasis was the most common. However, this complication occurred the same number of times in the group with congenital and the group with acquired agammaglobulinemia.

These data suggest, however, that bronchiectasis may be more frequent in the acquired form of agammaglobulinemia than in the congenital type but they do not yet support the concept that a bronchiectasis-agammaglobulinemia syndrome is an entity. Janeway, however, has stated that in his experience bronchiectasis is the most common clinical manifestation of

TABLE III
Pulmonary Disease in Agammaglobulinemia

Type of Agammaglobulinemia	No. Cases	No. Reported Pulmonary Infections	No. Pulmonary Complications
Congenital Agammaglobulinemia	24	24 reported*	4 bronchiectasis
Acquired Disease	19	13 reported*	7 severe pulmonary complications, empyema, calcification, bronchiectasis

*All cases without pulmonary disease incompletely reported.

acquired agammaglobulinemia. This has not been our experience since neither of our cases of acquired agammaglobulinemia had bronchiectasis while one of our children with congenital agammaglobulinemia suffered from bronchiectasis. Until reporting is both more extensive and more complete it seems worthwhile merely to recognize the relative frequent occurrence of bronchiectasis in patients with both the congenital and acquired forms of agammaglobulinemia.

Of the eight cases of agammaglobulinemia studied at the University of Minnesota and Ancker Hospitals, six were of the congenital variety and two were acquired. All the patients with congenital agammaglobulinemia were males. Five of these patients presented histories of severe recurrent pulmonary infections with many attacks of pneumonia being diagnosed in each patient. In the sixth case, a sibling of a proved case of agammaglobulinemia, the protein disturbance was discovered when the baby was three months old. Except for one episode of diffuse respiratory disease, this child has been kept free of disease by treatment with prophylactic antibiotics and gamma globulin for approximately one year. In the two cases

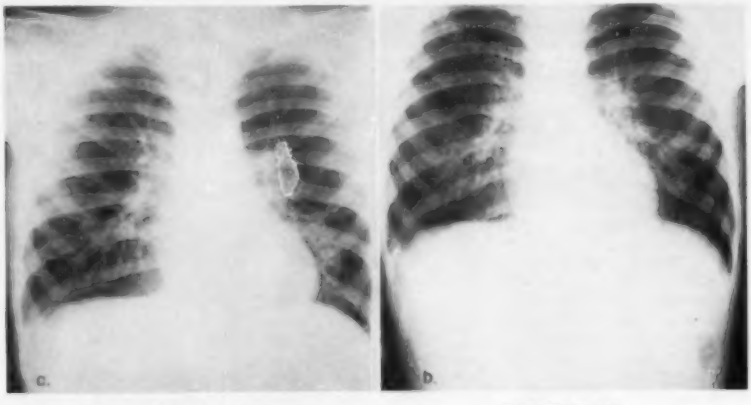

FIGURE 1A FIGURE 1B

Figure 1: Episode of pneumonia in a patient with congenital agammaglobulinemia. Note the pericardiac infiltration of the pulmonary parenchyma. This episode of pneumonia was associated with the presence of Type VII pneumococci in the sputum and nasopharynx. Note the clearing of the process in *Figure 1B*. It may be further seen that the many attacks of pneumonia which this patient has had have not produced roentgenologically apparent damage to the pulmonary parenchyma.

of adult or acquired type of agammaglobulinemia, the disease presented as a syndrome featured by recurrent attacks of pneumonia and pneumonitis. Meningitis, otitis media, and sinusitis were also recurrent problems in these patients. Two of our total group of eight agammaglobulinemic patients developed pulmonary complications secondary to pneumonia. One of the children having bronchiectasis was unsuccessfully treated by right lower lobectomy and the process has extended to involve virtually the entire remaining portions of the right lung at the present time. One of the adults shows persistent diffuse pulmonary radio-densities at the lung bases bilaterally. These have been interpreted as indicating the presence of residual pulmonary fibrosis resulting from 34 attacks of pneumonia over an eight year period. Two children in whom agammaglobulinemia was associated with a blood dyscrasia featured by agranulocytosis died of pulmonary disease, post mortem examination revealing in each instance interstitial pneumonitis and bronchopneumonia. In neither of these cases was the diagnosis of agammaglobulinemia made antemortem but rather the diagnosis became apparent later when stored serum was analyzed electrophoretically.

The following case summaries emphasize the importance of recognizing numerous bouts of pneumonia, episodes of septicemia and meningitis as manifestations of the immunologic deficiency associated with failure of gamma globulin formation.

Case 1: E. S., a seven year old boy was well until seven months of age, when he developed diarrhea and pneumonia. This infection responded rather promptly to treatment with sulfonamides. Subsequently he has had at least eight episodes of pneumonia, sometimes bronchial, sometimes lobar, in character. He was almost constantly ill, suffering at different times from numerous attacks of middle ear infection, sinus infection, three attacks of meningitis, repeated urinary tract infections, and septicemia. The microorganisms responsible for the infections have included pneumococci, hemophilus, meningococci and proteus. A severe episode of laryngotracheobronchitis, one year prior to the beginning of our study, necessitated tracheotomy. On Figure 1A is shown a PA film of the chest taken during a typical episode of pneumococcal pneumonia in this patient. Complete clearing of the density is illustrated in Figure 1B as is the absence of residual parenchymal damage in spite of the many attacks of pneumonia.

Case 2: W. A., a six year old white male was well until seven months of age when he developed meningitis. Treatment with penicillin and sulfadiazine resulted in recovery. During the first four years of life he had seven episodes of pneumonia. Several attacks of pneumonia occurred during 1953 following which bronchiectasis was discovered in the right lower lobe. Figure 2A illustrates the PA view of the chest taken at that time. Right lower lobectomy was performed which resulted in slight clinical improvement. However, during the subsequent year he had several additional attacks of pneumonia, numerous episodes of middle ear and sinus disease. Atelectasis and infiltration developed in the remaining portions of the right lung (Figure 2B) and bronchograms, (Figure 2C) showed that the bronchiectasis had extended to involve both the remaining upper and middle lobes on the right. Bronchograms of the left lung were normal. In Figure 3A is shown a medium power microscopic view of a typical area from the excised right upper lobe of the lung. On this photomicrograph the chronic inflammatory reaction and bronchiectatic process involving medium sized bronchi is illustrated. Under lower power view the inflammatory reaction at this site seems no different from that observed in bronchiectasis occurring in other patients. In Figure 3A high power views of the bronchiectatic process in the agammaglobulinemic patient is compared to high power view of the inflammatory process of an immunologically normal patient with bronchiectasis (Figures 3C and 3D). The absence of plasma cells in the chronic inflammatory exudate of the agammaglobulinemic patients represents a striking contrast to the marked plasmacytosis in those non-agammaglobulinemic subjects.

Case 3: T. A., a 12 month old child sibling of W. A. was discovered to be agammaglobulinemic at three months of age as a consequence of performance of electrophoretic

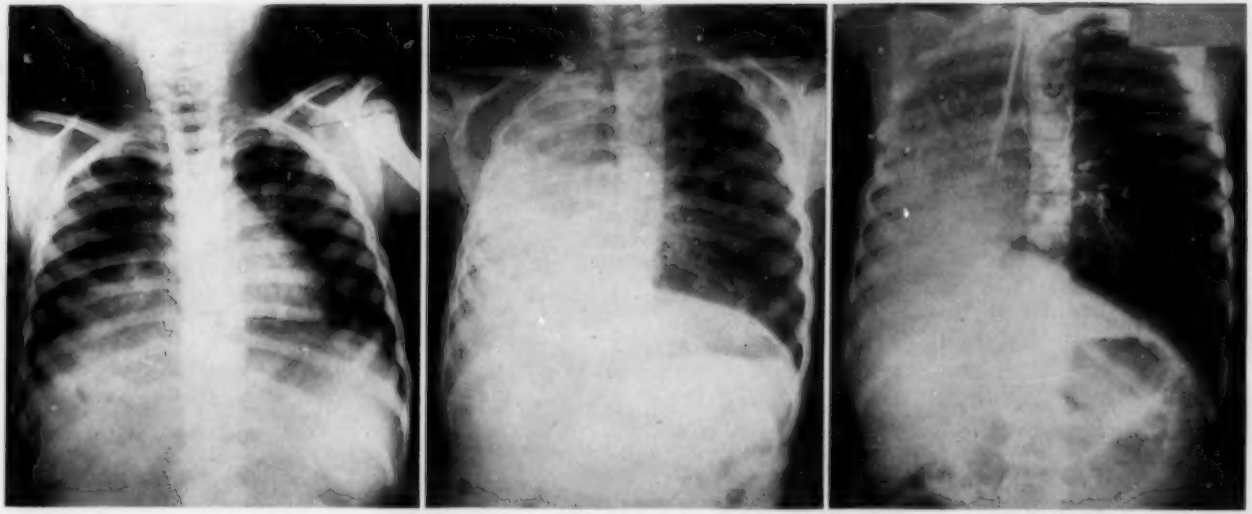

FIGURE 2A FIGURE 2B FIGURE 2C

Figure 2A: Bronchiectasis in patient with congenital agammaglobulinemia. Infiltration of the right lower lobe diagnosed clinically and roentgenologically as bronchiectatic process.—*Figure 2B:* One year following surgical resection of right lower lobe. Chronic infiltrative process has extended to involve almost the entire right lung. Note evidence of atelectasis as well as the infiltrative process.—*Figure 2C:* Bronchogram showing saccular and tubular bronchiectasis of the right middle and right upper lobes. There is no evidence of bronchiectasis on the left.

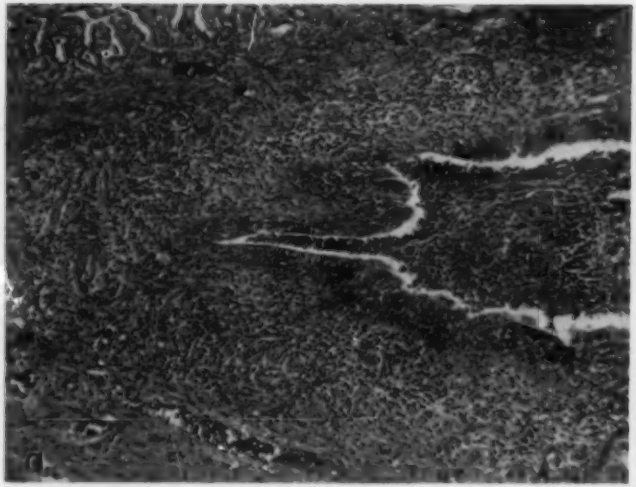

FIGURE 3A

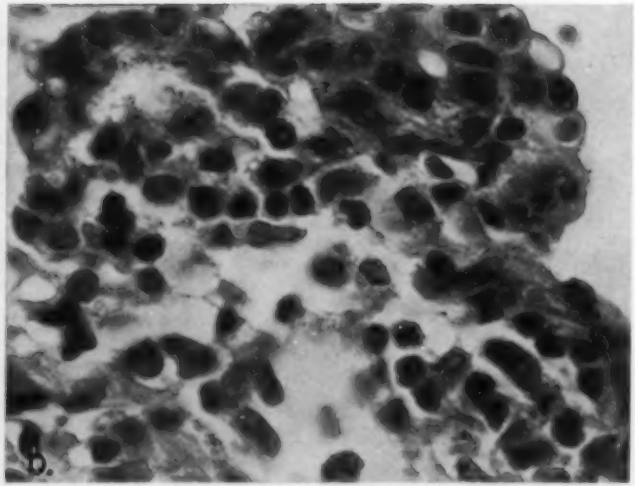

FIGURE 3B

Figure 3A: A X200 illustration of the bronchiectatic process in the right lower lobe removed surgically from patient with agammaglobulinemia. Note the extensive inflammatory exudate and the involvement of the bronchial wall.—*Figure 3B:* X800 high power view of the inflammatory exudate in the bronchiectatic lung in the patient with agammaglobulinemia. Note the infiltration by mononuclear cells and lymphocytes. Plasma cells are lacking.

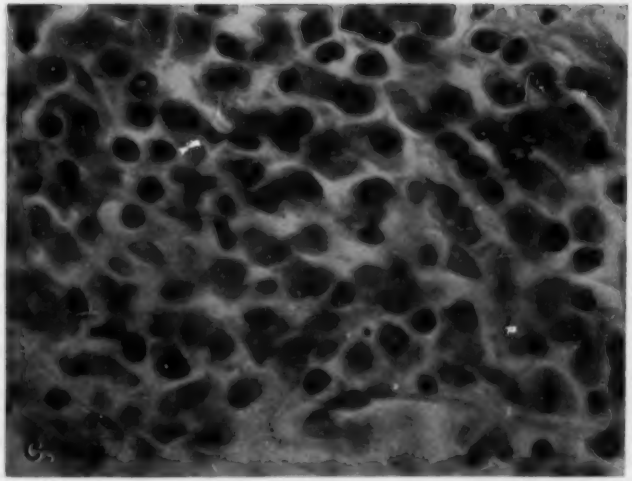

FIGURE 3D

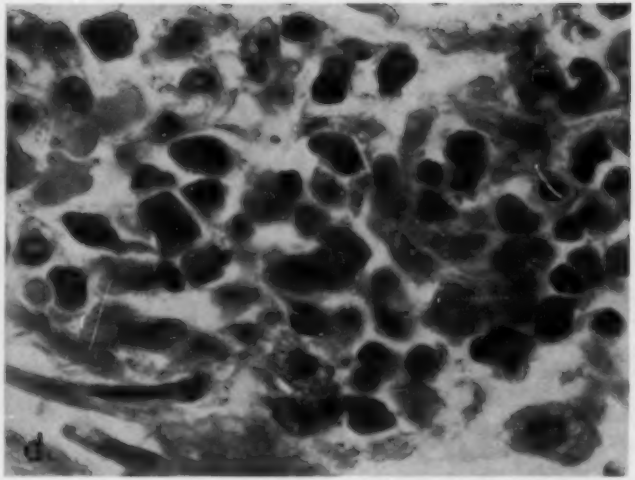

FIGURE 3C

Figure 3C: Bronchiectasis in an immunologically normal person. Note the abundant plasmacytosis which is characteristic of this kind of "chronic inflammatory process." *Figure 3D:* Plasmacytosis in bronchiectatic lung of another immunologically normal patient. The dirth of plasma cells in the inflammatory exudates of the patients with agammaglobulinemia represents a striking reflection of the immunological handicap.

analysis on serum specimens from all the members of his family. He was treated with prophylactic broad spectrum antibiotics during a period of intensive study and recently has been maintained on gamma globulin administration every few weeks. During a period prior to gamma globulin therapy, after antibiotics had been discontinued, he developed otitis media and a bacterial respiratory infection shown to be due to pneumococci. The latter disease responded promptly to treatment with penicillin.

Case 4: F. T., a 20 month old child, was well until seven months of age, when onset of pneumonia occurred, and during the ensuing months he experienced 10 recurrent attacks of pneumonia. He expired during an episode of recurrent pulmonary infection and autopsy findings showed extensive interstitial pneumonia. In addition to agammaglobulinemia evidence was obtained indicating that the child had cyclic or intermittent neutropenia.

Case 5: T. T., a 15 month white male sibling of F. T., Case 4, had many severe episodes of pneumonia beginning when he was six months old. Persistent neutropenic was present in addition to the agammaglobulinemia. He died during one episode of pneumonia due to a resistant staphylococcus prior to the recognition of the true nature of his disease. In both of the latter two cases agammaglobulinemia was demonstrated on both paper and free electrophoresis of the serum.

Case 6: J. S., 10 month old white male had pneumonia at three months of age, which responded to therapy. Pneumonia recurred at five months of age and again when the child was six months old. Study of the child's serum when he was seven months old revealed the presence of agammaglobulinemia.

In the acquired type described below, the incidence of recurrent pulmonary disease is even more striking than that noted in the congenital type. Although cases of bronchiectasis have been reported by others, the only pulmonary complication noted in our patients was residual interstitial fibrosis of the right middle lobe in one case.

Case 7: F. H., was a 58 year old white male who was well until four years prior to study when he began to have recurrent attacks of pneumonia. A mediastinal mass was discovered and in 1951 a 540 gram thymoma was removed. A serum protein determination done just prior to surgery was 5.1 grams per cent. The tumor showed generalized proliferation of all the thymic elements, particularly benign proliferation of the thymic reticulum. In Figure 4A is illustrated the chest film of F. H. taken prior to surgery in 1951. The huge mediastinal mass is to be noted. Figure 4B shows chest film after surgery. During the three years following excision of the thymoma this patient suffered from recurrent episodes of pneumonia usually beginning with chills, high fever, and cough. The development of rusty sputum was commonly noted. The patient himself stated that because of his recurrent pulmonary disease he became virtually addicted to terramycin, carrying a bottle of capsules with him wherever he went. That the agam-

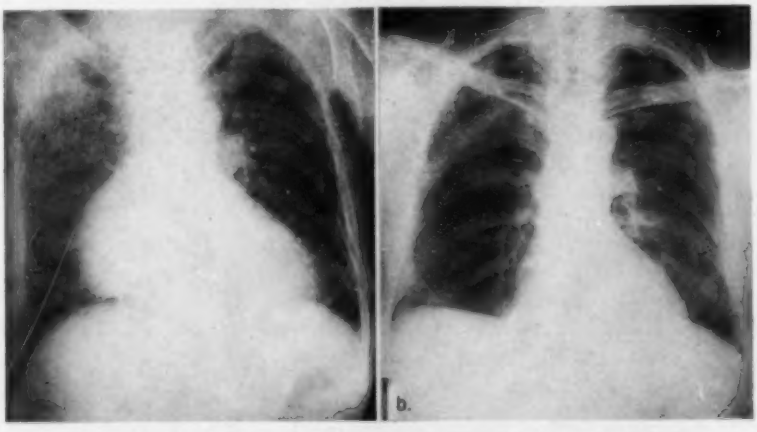

FIGURE 4A FIGURE 4B

Figure 4: Tumor of thymus in patient with acquired agammaglobulinemia.—*Figure 4A:* X-ray films of the chest showing the mediastinal mass which upon surgical excision turned out to be a 540 gram benign thymoma—prior to surgical intervention.—*Figure 4B:* Following surgical removal of the thymus tumor. Note complete absence of the mediastinal mass.

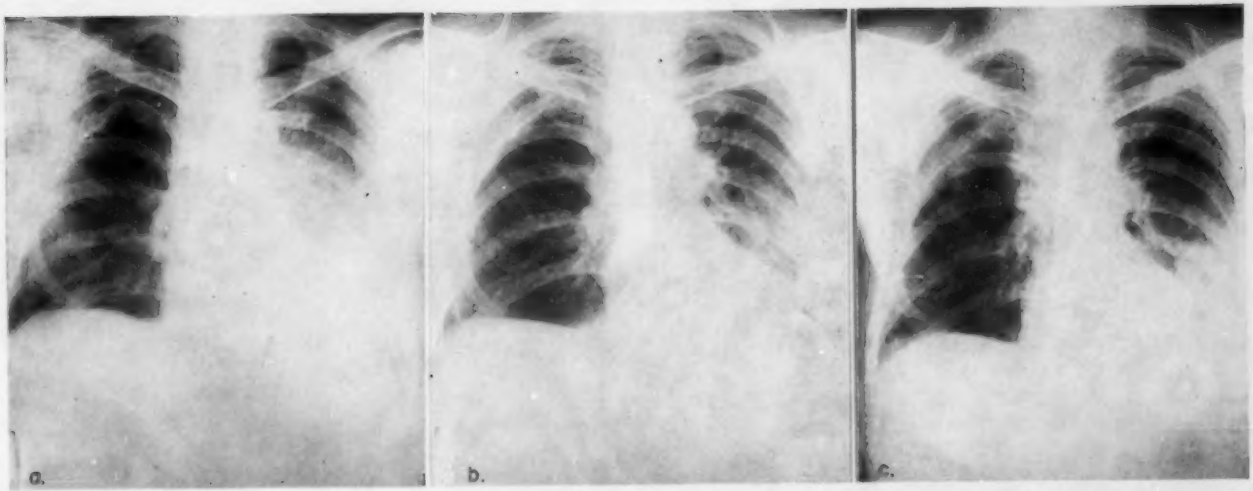

FIGURE 5A FIGURE 5B FIGURE 5C

Figure 5: Pulmonary infiltrations in 58 year old male with acquired agammaglobulinemia.—*Figure 5A:* Note lobar consolidation in left lower lobe.—*Figure 5B:* Clearing of process in left lower lobe.—*Figure 5C:* Reinfiltration of process in left lower lobe 6 months after first. During a four year period following the development of his disease this man had at least 17 episodes of pneumonia several times associated with pneumococcal infection.

maglobulinemia was present at the time the thymoma was discovered is suggested by the observation that a total serum protein determination done at the time of his first hospital admission was 5.1 gram per cent, a value identical to that observed when the agammaglobulinemia was known to exist. Additional support for this conclusion was the fact that he had three episodes of pneumonia during the three month period following discovery of the tumor and its ultimate removal. Figures 5A, 5B and 5C illustrate the pulmonary infiltrations which featured the recurrent respiratory infections this patient suffered following the development of his clinical disease. In all, he had at least 17 separate attacks of bacterial pneumonia during the four years of his illness.

Case 8: L. L., 30 year old white female was well until eight years prior to study. With no apparent precipitating cause she began to have many severe bacterial infections. During the eight years of her disease she has had 34 episodes of pneumonia, sometimes lobar and other times bronchial in character. In addition to pneumonia, repeated episodes of otitis media, sinusitis, four attacks of pneumococcal meningitis and other severe bacterial infections kept this patient in almost constant need of medical and hospital care. Figure 6A shows the chest x-ray revealing pneumonia described by the roentgenologist as being limited primarily to the right perihilar region. This infection was associated with high fever, leukocytosis and the presence of pneumococci in her nose culture and sputum. Figure 6B shows her lungs during a separate episode of bilateral basilar pneumonia. A more characteristic lobar distribution is seen.

In Figure 7A the chest film reveals interstitial fibrosis following a six month period when she was kept free of demonstrable respiratory infection by continuous prophylactic antibiotic therapy. During this entire period she was free from recurrent pneumonia that had been a virtually constant problem since her illness began approximately eight years before. Bronchograms illustrated in Figure 7B indicate clearly that bronchiectasis has not yet occurred and does not account for the apparent fibrosis on the roentgenograms. This observation indicates further that adults with acquired agammaglobulinemia may have innumerable episodes of pneumonia without developing bronchiectasis. Similarly our other case of acquired agammaglobulinemia, F. H., had 17 attacks of bacterial pneumonia over a four year period without developing bronchiectatic changes.

Interestingly enough, both L. L. and F. H. had a hematological disorder associated with the agammaglobulinemia syndrome. As already mentioned with F. H., a benign thymoma featured by hyperplasia of the thymic reticulum was present. In the case of L. L. a diffuse hyperplasia of the fixed and free reticulum (mesenchyme) of the

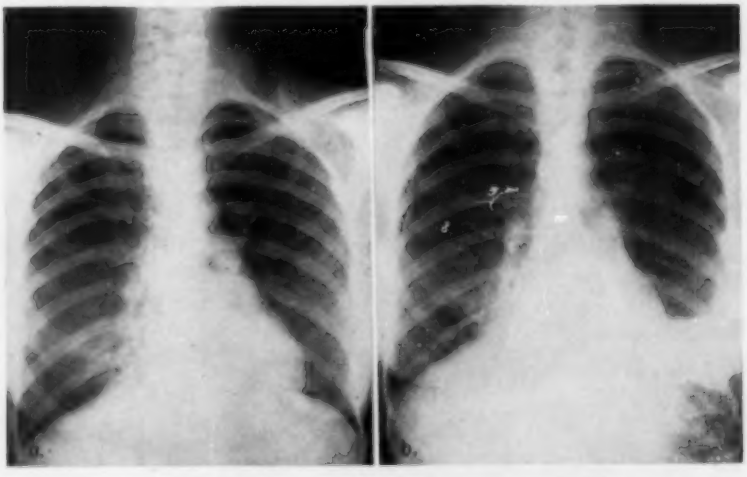

FIGURE 6A FIGURE 6B

Figure 6A: Bilateral pneumonia in 30 year old female with acquired agammaglobulinemia. Note infiltration at lung bases bilaterally.—*Figure 6B:* Recurrence of pneumonia this time with more of a lobar configuration at left base. Over an eight year period this patient suffered at least 34 attacks of pneumonia, four attacks of meningitis and numerous other episodes of bacterial infection.

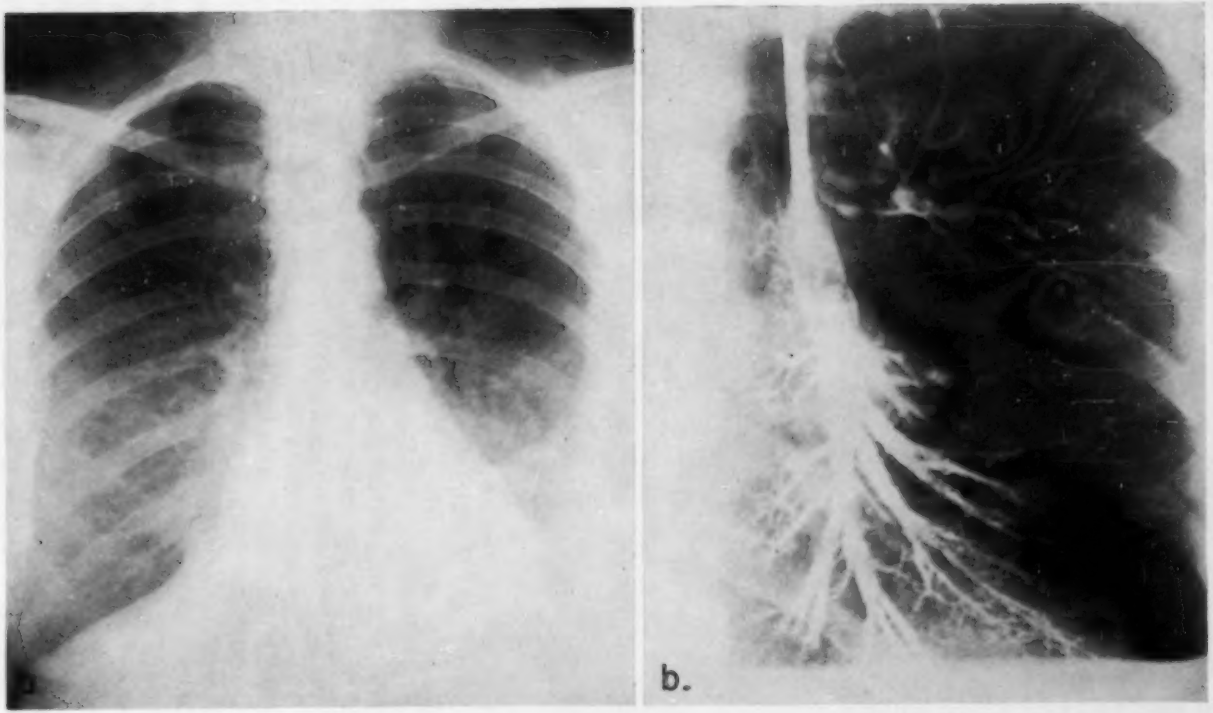

FIGURE 7A FIGURE 7B

Figure 7A: Residual "fibrosis" at the lung bases in patient whose earlier pneumonic episodes are illustrated in Figure 6.—*Figure 7B:* Bronchogram reveals the absence of bronchiectasis in the involved areas.

spleen, lymph nodes and bone marrow was present. In this instance hepatosplenomegaly was associated with the development of a Coombs-negative acquired hemolytic anemia and leukopenia. Splenectomy resulted in prompt disappearance of the hemolytic anemia. This observation of acquired hemolytic anemia in a patient incapable of antibody formation coupled with its dramatic cure by splenectomy is strong evidence in support of the concept of hypersplenism independent of immunological mechanism. An entirely similar case has been reported by Rhon et al.[15] Microscopic study of the spleen revealed the same abnormality of the reticulum observed from study of the bone marrow and lymph nodes—namely a diffuse proliferation of the reticular stroma and the occurrence of a granulomatous process not further defined by the pathologist. These findings will be presented in greater detail in another report.[16]

At the present time this patient is being maintained on continuous prophylactic treatment with penicillin and terramycin and during the past one and one-half years has been completely free of the recurrent bacterial infections which had been such a serious problem during the previous eight years.

Discussion

The relatively new disease agammaglobulinemia has been described from the point of view of the chest physician. Virtually all of the patients suffering from this disease present themselves to the doctor because of recurrent pulmonary infections. Many of them, both children and adults, suffer severe complications of their pulmonary infections namely bronchiectasis, empyema, lung abscess, atelectasis and pulmonary fibrosis. These observations make it particularly important for those concerned with the management of pulmonary disease to be aware of agammaglobulinemia, to make the diagnosis early and to institute treatment which will minimize the symptomatology and perhaps prevent the destructive consequences of recurrent severe bacterial disease of the pulmonary parenchyma.

It is now recognized that at least three forms of agammaglobulinemia exist. The disease first described by Bruton is a childhood form of agammaglobulinemia which occurs only in males and is transmitted as a sex-linked recessive trait. To date 24 cases of this form of agammaglobulinemia have been reported. In addition, and apparently distinct, is the form of agammaglobulinemia occurring in adults. This disease appears to occur at any age in either sex. Nineteen such cases have now been reported bringing the total number of agammaglobulinemic patients already described in the clinical literature to 43. The third type of agammaglobulemia is a transient form which occurs in infants during the first six months of life. This form represents a delay in assumption by the infant of gamma globulin formation. Although several cases of the latter disease have been recognized,[43-45] little critical information has so far been presented concerning this disturbance. It has, however, been suggested that this transient hypogammaglobulinemia of infancy may be associated with the pulmonary disease responsible for many unexpected or "crib" deaths occurring in infants.

In both the congenital and adult forms, the isolated deficiency of gamma globulin in the blood is associated with failure of the immune response which probably accounts for the extreme susceptibility of the patients with this metabolic disorder to bacterial disease, and accounts for the characteristic expression of the clinical syndrome.

Recent studies[3, 9] have indicated that underlying the deficiency of gamma

globulin and antibody formation in these patients is a disturbance of the hematopoietic tissues expressed in a variety of ways but in each instance featured by the absence of plasma cells and failure of plasma cell development in response to antigenic stimulation. This concept receives support from observations presented in this paper. In immunologically normal persons bronchiectasis is associated pathologically with the infiltration of the pulmonary parenchyma by leukocytes of both polymorphonuclear and mononuclear type. In the pathological material of every case of bronchiectasis which we have examined, numerous plasma cells were to be found among the mononuclear cells in the inflammatory exudate. To the pathologist these cells are recognized as signs of the chronicity of the inflammatory process. In the bronchiectatic pulmonary tissue removed from a patient with agammaglobulinemia herein described, the inflammatory exudate differed from that of the immunologically normal bronchiectatic patients in one particular—plasma cells were not to be found in the exudate. This observation lends strong support to the concept that in some way gamma globulin production and antibody formation are intimately associated with plasma cell formation and strengthens the concept that occurring in inflamed tissues these cells are the sign of local antibody production. With the recognition of the disease, completion of its primary classification and delineation of its distinctive features, it seemed worthwhile to stress the prominent part played by pulmonary infection in the course of both congenital and acquired types. It seems doubtful from the data presented here that significant differences in the incidence of lower respiratory tract infections exist between the two groups. All patients with agammaglobulinemia regardless of the sub-classification are inordinately susceptible to pulmonary infections with pneumococci, streptococci, hemophilus and staphylococci and without prophylactic treatment their lives are one round of severe pulmonary disease after another. Whether the complicating pulmonary disorders, e.g. bronchiectasis, occur more commonly in the adult form of agammaglobulinemia than in the childhood disease awaits further reporting. From the data currently available and presented in our Tables it would appear that approximately 17 per cent of the congenital cases thus far reported have developed bronchiectasis whereas 30 per cent of the adult cases which have been completely reported to date have had this complication. Personal communications[57] concerning unreported and incompletely reported cases indicate that bronchiectasis may occur even more frequently in the adult disease than our summary would indicate. Contrariwise there is also a suggestion that our figures may be somewhat high for patients with the congenital disorder. Only future complete reporting will clarify this relationship. The fact that bronchiectasis does occur with considerable frequency in both the adult and childhood forms of agammaglobulinemia suggests, however, that it might be prudent to carry out electrophoretic analysis on serums of all patients with bronchiectasis particularly if the latter disease develops during adult life in an effort to ferret out the cases of agammaglobulinemia being expressed in this way.

Both of our cases of the acquired type of agammaglobulinemia had overt disease of the reticuloendothelial system. In one instance a huge benign tumor of the thymus was observed while the other case was featured by diffuse proliferation of the reticulum resulting in lymphadenopathy, hepatosplenomegaly and reticular hyperplasia of the bone marrow associated with hypersplenism. Just as was the case with the agammaglobulinemic children, neither of these patients was capable of plasma cell proliferation in response to antigenic stimulation. On the basis of the uniform occurrence of diverse hematological disturbances in patients with agammaglobulinemia including profound lymphopenia, neutropenia, eosinopenia, reticular hyperplasia, and thymic tumor, it has been postulated that the basic disease in both congenital and acquired agammaglobulinemia resides in a disordered reticular function which is expressed in all of the patients as a failure of antibody and gamma globulin production associated with failure of development of plasma cells from reticular cells—their natural precursor.

In sharp contrast to the extreme susceptibility of these patients to bacterial disease as documented in this and previous reports, virus diseases have not presented a serious problem. This paradox features both the congenital and the acquired forms of agammaglobulinemia.

For example, even with thorough re-exposure on numerous occasions, recurrences of measles, chickenpox and mumps have not been a problem and these patients do not appear to have any special difficulty with the common respiratory diseases or atypical pneumonia. The explanation for this relative resistance to virus infection has not been elucidated, nor is it certain that the resistance extends to all viruses. Suggesting that some virus infections may be poorly handled by these patients just as are bacterial infections is the fact that each of two patients with agammaglobulinemia known to have developed virus hepatitis died. In one of the patients fatal acute yellow atrophy of the liver resulted[53] whereas the other succumbed after a prolonged illness diagnosed as chronic hepatitis.[54]

Although much has been accomplished through treatment of patients with agammaglobulinemia the therapeutic approaches available are not yet entirely satisfactory. Replacement therapy in the form of injections of gamma globulin appears to be particularly beneficial in children. As usually carried out 0.6 cc. of concentrated gamma globulin solution containing 0.1 gram of gamma globulin per kg. of body weight is given intramuscularly. This dosage serves to bring the circulating gamma globulin concentration to levels approximating 100 mg. per cent which appear to be protective against many of the common bacterial infections. Since the half life of gamma globulin in these patients is approximately 30 days[8, 11, 22] injections must be given every three or four weeks in order to provide continuous protection in this way.

The reported failure[10] of gamma globulin to provide clinical improvement in adults or children[17] with agammaglobulinemia is probably due in part at least to the use of insufficient quantities of gamma globulin. Prophylaxis with antibiotics has been advocated for these patients,[10] an

approach which would be supported by our experience with L. L. This patient having an average of 4-6 attacks of pneumonia and many other severe infections each year has been kept free of bacterial infections for a period of one and one-half years through the use of prophylactic therapy with terramycin in a dosage of 15 mg./kg./day. Similarly, one of the children in whom the agammaglobulinemia is complicated by bronchiectasis, continuous administration of three antibiotics provided in rotation has resulted in striking clinical improvement which was not achieved by gamma globulin alone.

On theoretical grounds we hesitate to recommend reliance on antibiotics to protect these patients from recurrent bacterial disease. We fear the establishment of a potentially threatening flora of microorganisms resistant to available antibiotics in these patients who are characterized by a deficiency in one of the major defense mechanisms. However, with the ever increasing number of broad spectrum antibiotics available, ultimately a combination of prophylactic antibiotic and gamma globulin therapy may prove to be the most efficacious approach to this problem.

To those concerned with the mechanism underlying this disease agammaglobulinemia represents a challenging experiment of nature.[3, 9] The ultimately successful management of these patients must await more basic information on the nature of both the inherited and acquired forms of this molecular disease.

SUMMARY

1. Agammaglobulinemia—a relatively new disease is discussed from the standpoint of the chest physician.

2. Eight cases studied at the University of Minnesota during the past two years are briefly presented.

3. The available literature on agammaglobulinemia is reviewed to emphasize the importance of pulmonary manifestations in the clinical expression of this metabolic disorder.

4. Among the 43 cases reported to date, 24 have been of the congenital type which is transmitted as a sex-linked recessive trait and 19 have been of the acquired type.

5. The most consistent clinical finding in both groups of agammaglobulinemic patients is recurrent bacterial respiratory infection often expressed as lobar or bronchiopneumonia.

6. Bronchiectasis occurred in four of 24 cases of congenital agammaglobulinemia and four of 13 completely reported cases of acquired agammaglobulinemia.

7. Other pulmonary complications reported to date in agammaglobulinemic patients include empyema, lung abscess, atelectasis, pulmonary fibrosis and diffuse pulmonary calcifications.

8. The inflammatory exudate of the bronchiectatic processes of an agammaglobulinemic patient and of immunologically normal persons are compared. The characteristic absence of plasma cells from the exudate in the agammaglobulinemic patient is recorded.

9. The development of "acquired" agammaglobulinemia associated with the occurrence of a large thymoma in a 54 year old male is described.

10. The hematological basis of agammaglobulinemia is mentioned.

11. The therapeutic approach to agammaglobulinemia is discussed.

RESUMEN

1. La agamaglobulinemia es una enfermedad relativamente nueva que se discute aquí desde el punto de vista del especialista de tórax.

2. Se presentan de manera breve ocho casos que han sido estudiados en la Universidad de Minnesota durante los dos años pasados.

3. Se hace una revisión de la literatura sobre la agamaglobulinemia para hacer resaltar la importancia de las manifestaciones clínicas que expresan este trastorno metabólico.

4. Entre los 43 casos que se han relatados hasta ahora, 24 han sido de tipo congénito que es trasmitido como un carácter recesivo ligado al sexo y en 19 se ha encontrado que son adquiridos.

5. El hallazgo más constante clínicamente en ambos grupos de agamaglobulinemia es la infección respiratoria recurrente a menudo expresada como neumonía lobar o bronconeumonía.

6. Ocurrió la bronquiectasia en 4 de 24 casos de agamaglobulinemia congénita y 4 de 13 de los relatados completamente entre los de agamaglobulinemia adquirida.

7. Otras complicaciones pulmonares que se han relatado hasta ahora son: empiema, absceso pulmonar, atelectasia, fibrosis pulmonar y calcificaciones pulmonares difusas.

8. Se ha comparado el exudado inflamatorio de los procesos bronquiectásicos de un enfermo de agamaglobulinemia y los de un enfermo que es normal en el aspecto inmunobiológico. Se refiere la ausencia característica de células plasmáticas en el exudado del enfermo con agamaglobulinemia.

9. Se describe el desarrollo de una agamaglobulinemia "adquirida" concurriendo con un timoma grande en un hombre de 54 años.

10. Se menciona la base hematológica de la agamaglobulinemia.

11. Se discute la conducta terapéutica en la agamaglobulinemia.

RESUME

1. Les auteurs discutent du point de vue du spécialiste des poumons "l'agammaglobulinémie," maladie de découverte relativement récente.

2. Ils présentent brièvement huit cas étudiés à l'Université de Minnesota pendant les deux années qui viennent de s'écouler.

3. Ils font la revue de la littérature actuelle portant sur l'agammaglobulinémie, en insistant sur l'importance des manifestations pulmonaires dans l'expression clinique de ce trouble métabolique.

4. Parmi les 43 cas rapportés récemment, 24 ont été du type congénital, transmis comme un caractère récessif, et 19 ont été du type acquis.

5. La constatation clinique la plus caractéristique dans les deux groupes de malades atteints d'agammaglobulinémie est l'infection respiratoire bactérienne récidivante, souvent de type lobaire ou prenant la forme bronchopneumonique.

6. Une bronchiectasie survint dans 4 des 24 cas d'agammaglobulinémie congénitale, et dans quatre des 13 cas d'agammaglobulinémie acquise, rapportés en détail.

7. Les autres complications pulmonaires rapportées chez des malades atteints d'agammaglobulinémie, sont: l'épanchement pleural, l'abcès pulmonaire, l'atélectasie, la fibrose pulmonaire et des calcifications pulmonaires diffuses.

8. Les auteurs ont comparé l'exsudat inflammatoire des processus bronchiectasiques d'un malade atteint d'agammaglobulinémie, et de personnes immunologiquement normales. Ils rapportent l'absence caractéistique de plasmocytes dans l'exsudat du malade atteint d'agammaglobulinémie.

9. Les auteurs décrivent le développement d'une agammaglobulinémie acquise associée à l'apparition d'un thymome important, survenus chez un malade âgé de 54 ans.

10. Les auteurs mentionnent la base hématologique de l'agammaglobulinémie.

11. Ils discutent la conduite thérapeutique.

ZUSAMMENFASSUNG

1. Die Agammaglobulinämie, eine verhältnismässig neue Krankheit, wird vom Standpunkt des Thoraxspezialisten erörtert.

2. Acht während der letzten zwei Jahre an der Universität von Minnesota untersuchte Fälle werden kurz dargestellt.

3. Es wird ein Überblick über die verfügbare Literatur über Agammaglobulinämie gegeben, um die Bedeutung der Lungenerscheinungen im klinischen Bilde dieser Stoffwechselstörung hervorzuheben.

4. Von den bisher veröffentlichten 43 Fällen waren 24 kongenitaler Art, die als eine sechsgliedrige rezessive Anlage fortgepflanzt wurden, und bei den übrigen 19 handelte es sich um die erworbene Form.

5. In beiden Gruppen der Kranken mit Agammaglobulinämie ist der wichtigste Befund eine zu Rückfällen neigende respiratorische bakterielle Infektion, die häufig in Form einer lobären oder einer Bronchiopenumonie zum Ausdruck kommt.

6. Bronchiektasen traten in vier der 24 kongenitalen Agammaglobulinämien und in vier weiteren unter 13 erworbenen Fällen, über die ein vollständiger Bericht vorliegt, auf.

7. Zu weiteren Lungenkomplikationen, die bisher in Fällen von Agammaglobulinämie beschrieben wurden, gehören Empyem, Lungenabszess, Atelektase, Lungenfibrose und diffuse Kalkablagerungen in der Lunge.

8. Das entzündliche Exsudat aus bronchiektatischen Veränderungen. eines an Agammaglobulinämie leidenden Kranken wird mit dem immunologisch normaler Personen verglichen. Bei dem Kranken mit Agammaglobulinämie wird ein charakteristisches Fehlen von Plasmazellen im Exsudat festgestellt.

9. Es wird der Fall eines 54 jährigen Mannes beschrieben, bei dem gleichzeitig eine "erworbene" Agammaglobulinämine und ein grosses Thymom beobachtet wurden.

10. Die hämatologische Grundlage der Agammaglobulinämie wird erwähnt.

11. Wege zur Behandlung der Agammaglobulinämie werden erörtert.

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Treatment of Acute Coronary Occlusion*

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Introduction

During the past thirty years, the diagnosis of acute coronary occlusion has been greatly facilitated and its treatment has been greatly improved. The diagnosis has been improved by the routine use of 12 electrocardiographic leads and by the recognition of atypical symptoms. Numerous mild cases have, thereby, been discovered and a broader understanding of the disease has been reached. It should be emphasized that at the onset of the attack, possibly because the artery has not yet been completely occluded, the electrocardiogram may be normal or may show only slight changes. At this time, RS-T depression may occur, as in coronary insufficiency, instead of the expected RS-T elevation.[1] The RS-T elevation may not appear for hours, and the Q-waves only later, at the end of one to two days. The treatment of the disease has been improved by several major therapeutic advances. These include oxygen therapy, a low calorie diet,[2, 3] the judicious use of digitalis and quinidine, the avoidance of such drugs as Adrenalin, nitroglycerin, camphor and strychnine, and the employment of anticoagulants.[4, 5] Recently, Levine has advocated the chair treatment of coronary occlusion.[6]

In 1935, the mortality rate in our private patients, during the first attack, was 10 per cent.[2, 3] Today, it is less than 5 per cent, among such patients, and is only 15 to 20 per cent during all attacks, among ward patients.

Treatment

Pain: The intensity of the pain, which ushers in the attack, is not an accurate gauge of the severity of the attack. Not infrequently, a coronary occlusion which begins with very severe pain runs a remarkably smooth course after the pain has eased. It is essential to relieve the pain as soon as possible. The most effective drug for this purpose is morphine; if the pain is intense, morphine should be given intravenously in a dose of eight or 10 mg. In most cases, with less severe pain, the subcutaneous administration of morphine, as well as of Demerol, Dilaudid or Pantopon is effective. In our experience, however, Demerol is much less efficacious than morphine. In very rare cases intravenous sodium amytal may give at least temporary relief. Oxygen and aminophylline (by vein or suppository) may be used but only rarely are efficacious in relieving the pain.

Nitroglycerin does not relieve the pain of acute coronary occlusion but

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is very effective in status anginosus, which represents a state of acute coronary insufficiency. It is distinguished from coronary occlusion by the finding of RS-T depression and/or T-wave inversion in the electrocardiogram. Reassurance, the free use of nitroglycerin and the administration of a narcotic, such as Dilaudid (1.5 to 2.5 mg.) three or four times a day, during a period of status anginosus often cause the pain to subside gradually and the patient may be asymptomatic for a long period. In other instances, however, status anginosus represents a premonitory phase of coronary occlusion. When the occlusion is complete, nitroglycerin no longer is effective and, indeed, is dangerous. Thus, nitroglycerin may be used not only therapeutically but also diagnostically.*

Hospital Vs. Home Care: As soon as the pain has been relieved, the advisability of hospitalization should be considered. If the conditions at home are satisfactory, the vast majority of patients can be treated at home, particularly since most attacks run a mild course following the initial pain. However, if the patient's condition is serious, if the home environment is unsuitable and if nurses are not available, the patient may be removed to the hospital immediately by ambulance.

At the onset of the attack, the patient is usually apprehensive. He may even be terrified; for, like many others, he may believe that the development of a coronary occlusion spells the end of things physically, sexually, socially and financially. Therefore, it is important to allay his fears at the first feasible opportunity, by assuring him that the vast majority of patients make a good recovery and can resume a full, productive life.

Anticoagulants: Less than 10 years ago anticoagulants were introduced in the treatment of coronary occlusion. Their use soon became routine unless a specific contraindication was present. Early reports indicated that a significant diminution in embolic complications and a lower mortality rate resulted therefrom.[5, 7-10] Great credit is due these early workers, Wright and others, for anticoagulants have been of great value in patients seriously ill with coronary thrombosis. During the past few years, however, several authors have questioned the value of anticoagulants in coronary occlusion[11] or have suggested that they were unnecessary in mild attacks.[12, 13] Russek and his co-workers found the mortality rate in good risk patients to be only 3.1 per cent, and the incidence of embolic phenomena to be only 0.8 per cent.[12] They reasoned, therefore, that the use of anticoagulants can, at best, decrease the mortality rate only 1 per cent, and that such a possible improvement is scarcely worth seeking, in view of the danger of hemorrhage. On the other hand, it has been suggested that all patients should receive the benefit of anticoagulant drugs, since the apparently mild case may develop embolic phenomena, or may suddenly develop congestive failure or shock. In view of the infrequency of these complications in mild cases, however, this does not appear to be a wise course to follow. We have found that in the vast majority of attacks which are considered mild during the first day or two, this judgment proves to be correct. If there is any question in the physician's mind at first, anticoagu-

*An increase in serum transaminase activity may prove of value in determining the presence of significant myocardial infarction at the onset of an attack.

lants may be administered for a day or two and then discontinued if the patient's course proves satisfactory. Naturally, should an indication for anticoagulant therapy arise at any time, it should be instituted immediately.

As the period of strict bed-rest in the treatment of coronary occlusion has been gradually shortened, not only in the mild but also in the more severe cases, the indication for anticoagulant therapy has further diminished since the major effect of anticoagulants is to reduce the incidence of phlebothrombosis, and early ambulation achieves the same end. In order to avoid phlebothrombosis, the patient should be urged to move his toes and legs and to take deep breaths early in the attack. Massage of the legs and the use of elastic stockings are beneficial.[14]

Anticoagulant drugs are indicated (1) when congestive failure or shock is present, (2) if there is evidence of or a history of phlebitis, (3) after a pulmonary embolus or infarction, and (4) following peripheral arterial embolism, with the exception of cerebral embolism. The age of the patient is not a factor in anticoagulant therapy; old age is not a contraindication to the use of anticoagulants. This is also true of pulmonary edema even if the sputum contains considerable blood.

Whether to use anticoagulants during the premonitory stage of acute coronary occlusion remains a moot question.[1, 15, 16] Although some success has been claimed for them in preventing the completion of the occlusion,[16] the data reported thus far appear insufficient and inadequately controlled. Our own results seem to indicate that anticoagulants neither prevent nor hasten the onset of coronary occlusion. At present, apparently no known treatment will prevent an impending attack.[17] The premonitory stage of coronary occlusion cannot be differentiated from acute coronary insufficiency, and since the majority of attacks of coronary insufficiency subside spontaneously, the efficacy of anticoagulants in the premonitory stage of occlusion is, necessarily, difficult to evaluate; for there is no way of knowing whether the drugs prevented the completion of an impending occlusion or whether no occlusion was impending.

If anticoagulants are employed in acute coronary occlusion, it is wise to give 50-75 mg. heparin intravenously, every four to six hours, for the first day or two, or 200 mg. Depoheparin every 12 hours intramuscularly. Oral therapy with Dicumarol, Tromexan[9, 10] or Hedulin is instituted simultaneously, since their effect is not manifest for one to three days. The initial dose of Dicumarol is 300 mg., followed by 100 to 200 mg. the second day and smaller daily doses thereafter, depending upon the prothrombin time. The effect of Tromexan is apparent in 18 to 24 hours but the individual reaction and daily dose are more variable than with Dicumarol. The dose is five or six times that of Dicumarol. Hedulin also acts more rapidly than Dicumarol. The initial dose is 200 to 300 mg. and the maintenance dose 50 to 100 mg. Final evaluation of this drug is not yet possible.

It is scarcely necessary to emphasize the extreme importance of careful supervision during anticoagulant therapy for hemorrhage, and even death may occur. While the response of most patients to anticoagulants is as

expected, that of others is entirely unpredictable. An initial 300 mg. dose of Dicumarol has, in some cases, prolonged the prothrombin time to dangerous levels, either within a day or two, or only after three or four days. Occasionally, bleeding occurs when the prothrombin time is well within therapeutic levels, i.e., 40 to 50 per cent of the control. Evidence of bleeding should be looked for in the urine, in the skin and elsewhere. Hemorrhage may occur into serous cavities, including the pericardium.[18] If bleeding occurs, vitamin K_1 oxide (50 to 100 mg.) intravenously will return the prothrombin time to non-dangerous levels within several hours. In the event of serious bleeding, the transfusion of fresh blood or plasma alone is effective.

When anticoagulants are administered, they should be continued for approximately one week after the patient has been permitted out of bed, and longer if there has been evidence of peripheral phlebitis or pulmonary infarction. Long-term anticoagulant therapy has been employed for months or years following an attack, but the value of this procedure has not been demonstrated as yet.

Anticoagulants are contraindicated in non-specific pericarditis since they are apt to cause bleeding into the pericardium in this condition. For this reason, it is essential to differentiate non-specific pericarditis from coronary occlusion. This can usually be done by means of the electrocardiogram; while ST elevations occur in both diseases, Q-waves are absent in pericarditis and usually are present in coronary occlusion. It has even been suggested, from experience in one or two cases, that anticoagulants should not be employed in coronary occlusion when a definite pericardial friction rub is present. We doubt the wisdom of this course. Anticoagulants are contraindicated in patients with a history of bleeding tendency, ulcerative colitis, peptic ulcer, renal or hepatic disease, and, probably, in those who have had a cerebrovascular accident.

Length of Bed Rest: When acute coronary occlusion first became widely recognized, and its diagnosis was commonly established, complete and prolonged bed-rest was the cardinal principle in therapy, although only scant data substantiated the need for such treatment.[19, 20] In the nineteen twenties and thirties it was generally believed that it took at least six weeks for a scar to form in the infarcted area and that, therefore, the patient should remain in bed for that period. However, in the early forties, many physicians, including ourselves, questioned the need for so long a period of bed-rest and shortened it for various empirical reasons: (1) "Silent" coronary occlusions were discovered in many patients whose electrocardiograms were typical of a previous coronary occlusion, yet who gave no history of previous attack. And, although they had had no bed-rest, their cardiac function was good and no evidence of aneurysm of the left ventricle was found. (2) Patients with known acute coronary occlusion who refused to stay in bed or insisted, openly or surreptitiously, on going to the bathroom from the first day, also showed no harmful effects of their activity. (3) Many patients whose course during the coronary occlusion was mild developed great anxiety and other psychological tensions because

of the prolonged rest in bed. This merely aggravated an otherwise mild illness and, occasionally, produced a prolonged psychoneurosis. For these reasons patients with mild attacks were often permitted to use a commode after the first two to three days and to sit in a chair after two to three weeks.

Great credit is due Levine,[6, 21-23] Dock[24] and Harrison[25, 26] for pointing out that prolonged bed-rest in acute coronary occlusion and in heart failure is often unnecessary, and, indeed, may be harmful. It has been shown that recumbency tends to increase cardiac work by increasing the circulating blood volume.[27, 28] In addition to the anxiety and depression it may produce, prolonged bed-rest leads to generalized loss of muscular and vascular tone, causes constipation and distention and predisposes to venous thrombosis. Conversely, chair treatment reduces these ill effects and lessens the need for prolonged anticoagulant therapy.

While many physicians now permit patients whose disease runs a mild course to sit in a chair after a shorter interval than before, Levine advocates the armchair treatment for all cases of acute coronary thrombosis, from the onset of the attack,[6] and particularly for patients with definite congestive failure. The patient is lifted or helped back into bed. Levine has reported patients with severe left ventricular failure who did not respond to treatment as long as they were kept in bed but who improved when they were placed in a chair. Recent confirmatory favorable reports on the chair method of treatment have appeared.[29, 30]

It seems to us that the most important principle in the therapy of coronary thrombosis is to *treat each patient individually*. The physical and psychological state of each patient should determine how he can best be treated. The patient suffering from a mild attack may be treated liberally, with every expectation of a good recovery. If such a patient is unable to use a bedpan it may be desirable to permit him to use a bedside commode and to sit in a chair from the very start. Or, he may be kept in bed for one week and then be permitted to sit up in a chair. During the period of bed-rest the patient should be given a small enema every second or third day. Such a short stay in bed does not engender any of the harmful sequelae of prolonged bed-rest. In mild attacks our own inclination is to keep the patient in bed approximately a week unless we think that earlier chair treatment is necessary to raise morale.

Patients who are more seriously ill (congestive failure, tachycardia, a systolic blood pressure below 80 or actually a state of shock) should be kept in bed until the usual therapeutic measures have been tried. Efforts should be made to approximate the sitting position by using a hospital-type of bed or by placing nine inch blocks under the headposts. If a patient fails to improve in spite of these procedures, he may be placed in a chair. There should not be too long a delay before chair treatment is instituted in these cases. Much controlled experience is necessary to determine the efficacy of the "armchair" treatment. But indiscriminate prolonged bed-rest for all patients appears inadvisable.[31]

Ambulation and Return to Work: When the patient is permitted to walk about, depends to some extent upon when he sat up. In very mild cases,

we allow walking at the end of the second week or at the beginning of the third; usually the patient begins to walk the fourth week. Such patients may be ready to return to work within two or three months.[2, 32-34] In the more severe cases, rehabilitation is slower but many of these patients also can resume work in three to six months. Treatment must be individualized. We have found that four of every five patients are able to resume work following coronary occlusion and can lead productive lives for many years.[2, 32-34]

We do not depend upon the electrocardiogram as a criterion for determining the progress of the patient or for deciding when he may sit up, begin to walk or return to work.[35] If his clinical course is satisfactory, the patient may get up and walk even though the electrocardiogram shows marked alterations. Nor do we always wait for the electrocardiogram to become stable. If the electrocardiogram returns to normal, the outlook is usually excellent but the patient may also do very well, during and after the attack, even if the electrocardiogram is markedly abnormal or shows the changes of ventricular aneurysm, i.e., large Q-waves, persistent ST elevation and deeply inverted T-waves.[34] Nor do we place too much reliance upon the sedimentation time as a guiding factor in treatment. We have observed patients who were running a severe course of acute coronary occlusion, with little elevation of the sedimentation rate, and, on the other hand, patients with very high sedimentation rates whose course was mild. A woman of 63, for example, became asymptomatic and afebrile several days after the onset of the attack. Her first sedimentation rate was elevated to 95. After four weeks it was still 88 although she was ambulatory and felt well. We do not prolong the period of bed-rest because of an elevated sedimentation rate if the patient is doing well clinically. In some patients the sedimentation rate remains increased to 40 to 50 mm. for many months or even years following an occlusion, long after they have resumed working. The determination of the C reactive protein may prove more useful than the sedimentation rate. A normal ballistocardiogram in coronary occlusion usually indicates a good recovery, but the patient may be doing very well even when the ballistocardiogram is definitely abnormal. Of course, in people over 50 the ballistocardiogram may be abnormal in the absence of heart disease.

Heart Failure: Not uncommonly coronary occlusion sets in dramatically as an attack of pulmonary edema. The treatment of this condition is the same as if coronary occlusion were not present. Morphine intravenously or intramuscularly is usually efficacious but intravenous aminophyllin and strophanthin may be necessary. Aminophyllin must be administered very slowly, the dose being 0.5 mg. The initial dose of strophanthin K is 0.25 mg. Injection of 0.1 mg. may be repeated every hour until 1 mg. has been given in 24 hours. Oxygen under positive pressure, rotating tourniquets or phlebotomy if shock is not present, and an intravenous mercurial diuretic may be helpful. Occasionally, the inhalation of alcohol vapor has been found to be effective.[36] In patients with pulmonary edema anticoagulant therapy should be instituted even if the sputum is bloody.

In the persistent type of congestive failure, in coronary occlusion, the usual treatment is given. However, particular care is required to avoid digitalis intoxication which is more dangerous in the presence of acute infarction. It is possible that the infarcted myocardium is more irritable and more sensitive to digitalis, for many of the attacks of ventricular tachycardia encountered in coronary occlusion have followed the administration of digitalis. Aged patients are more sensitive to digitalis than the young, often requiring half the average dose or less. The earliest symptoms of digitalis overdosage are usually weakness, anorexia and abdominal pain. These appear before nausea, vomiting and diarrhea occur. Premature beats and any other type of arrhythmia may develop. Potassium is the most effective antidote for this condition. A convenient method of administering it is a liquid oral preparation, such as "Potassium Triplex," but it may have to be given intravenously.

In addition to the use of digitalis, the salt intake should be restricted and mercurial diuretics given. If the degree of failure is not severe, an oral diuretic such as Neohydrin or Diamox is often beneficial. Two or three tablets of Neohydrin are given daily. The dose of Diamox is one tablet (250 mg.) daily four or five times a week.

Shock: Mild transitory states of shock are very common at the onset of coronary occlusion. Sometimes, the shock is profound and persistent. In the past this has augured a fatal outcome in 80 or 90 per cent of the cases. However, several vasopressor drugs are now available and are occasionally effective if used early.[37-40] Among them are (1) Norepinephrine (Levophed), (2) Mephentermine (Wyamine), (3) Methoxamine (Vasoxyl), and (4) Neosynephrine. Recently Aramine has been studied in normal subjects.[41]

Norepinephrine must be given intravenously. The initial dose is four mg. per liter of five per cent glucose in water. This may be increased to eight, 16 or even 32 mg. if necessary, until the systolic blood pressure rises to 100 to 110. The advantages of Norepinephrine are the ability to regulate the height of the blood pressure by varying the dose and the speed of injection, the rapid disappearance of its effect and the absence of undesirable side actions, such as myocardial stimulation. During its use the blood pressure should be recorded frequently, not only to determine whether the dose is adequate but also to avoid an excessive rise in blood pressure. If congestive failure is present, the amount of intravenous fluid administered with the Levophed should not be excessive. The dose of Mephentermine (Wyamine) is 15 to 30 mg., given intravenously or intramuscularly, and repeated as often as indicated. The dose of Methoxamine (Vasoxyl) is 20 mg., intravenously or intramuscularly. The dose of Neosynephrine is one mg. intravenously or five to 10 mg. intramuscularly. The sooner the vasopressor drugs are employed, the better is the outlook. Unfortunately, however, even if the blood pressure is raised, only some of the patients recover.

The use of ordinary plasma and blood infusion or of intra-arterial transfusion has not proved effective in shock following coronary occlu-

sion.[42, 43] When there is an element of congestive failure associated with shock, intravenous strophanthin or other digitalis preparations may be effective.[37, 40] In the absence of failure, digitalis may be harmful in shock and should be avoided.

Arrhythmias: All types of arrhythmias are common in coronary occlusion. We do not use quinidine routinely to prevent them. Premature beats, atrial and nodal tachycardia and atrial fibrillation and flutter are often transitory. If they do not remit quickly, or if any degree of shock or heart failure is present, treatment in indicated. For frequent premature beats, quinidine or Pronestyl is given. Atrial or nodal tachycardia often responds to carotid sinus or eyeball pressure; if it does not, Neosynephrine, 0.5 mg. may be administered intravenously, particularly if the blood pressure is low. If Neosynephrine is effective, digitalis is given parenterally or orally. If necessary quinidine or Pronestyl may be given orally or intramuscularly.

Ventricular tachycardia should be treated promptly with either quinidine or Pronestyl, administered orally or intramuscularly. If these drugs are ineffective by these routes, Pronestyl may be given intravenously, if well diluted and injected slowly. Since intravenous Pronestyl is apt to cause a considerable drop in blood pressure, Lævophed may be administered simultaneously to maintain the blood pressure or Neosynephrine given as soon as indicated.

A-V block occurs not infrequently when the right coronary artery is occluded and the diaphragmatic surface of the left ventricle is infarcted. Partial A-V block usually requires no treatment but atropine may abolish it. Complete A-V block was at one time considered a very ominous finding but our recent experience has been much more favorable. The danger of complete A-V block lies in the development of Stokes-Adams seizures. They may result from asystole or ventricular fibrillation or both. When the seizures are caused by asystole, adrenalin is administered subcutaneously or, if necessary, intravenously in very small doses. Sublingual Isuprel, 10 mg. may also relieve the attack. Recently, Zoll has devised a machine, called the "Pacemaker," for external electric stimulation of the heart in cases of asystole. He has reported good results from its use.[44] If the Stokes-Adams attacks are caused by ventricular fibrillation, Isuprel should be employed; quinidine and Pronestyl are contraindicated since they may completely depress the ventricle. If asystole and ventricular fibrillation alternate in the same patient, Isuprel and the "Pacemaker" should be used. In recurrent Stokes-Adams attacks, secondary to complete heart block, adrenalin or Isuprel may be repeated as often as necessary and the "Pacemaker" may be applied for long periods.[44]

Diet: The low calorie diet has greatly improved the outlook during the attack of coronary occlusion.[1, 2] It decreases the work of the heart and prevents gastro-cardiac reflexes. During the first few days or weeks, 800 to 1200 calories daily suffice. Thereafter, the intake may be gradually increased.

Nausea and Vomiting: These symptoms are often very disturbing and may be serious. They may be prevented by abstinence from fruit juices, cold milk and spicy foods. Dramamine (50 mg.), Thorazine (10 to 25 mg.) or Marezine (25 to 50 mg.) given orally, intramuscularly or by suppository, is the most effective treatment. Sips of charged water and ginger ale may also be helpful. Fluids by mouth should be restricted and solids given. Since nausea and vomiting may be caused by digitalis, morphine, aminophylline, ammonium chloride or quinidine, these drugs should be temporarily discontinued. If the nausea and vomiting persist, however, administration of the drugs may be resumed, since congestive failure alone may cause nausea and vomiting, which may disappear only after further digitalization.

Particularly, if the patient has received much morphine, severe constipation and distention may set in. A cathartic should be given at night and an enema in the morning, if necessary. The patient must be warned not to strain at stool. In the presence of distention, fruit juices and cold milk should be avoided. Intramuscular prostigmine may be required.

Hiccough: Hiccough is usually frightening to the patient and it is extremely important to reassure him over and over again. If this is done, the hiccough almost always subsides. If it persists, various remedial procedures may be employed, all of which have proved successful at some time: rebreathing into a paper bag, Carbogen (five or seven per cent CO_2 and O_2 inhalations), chlorpromazine (Thorazine), quinidine intramuscularly, niacin or atropine intravenously, inhalation of amyl nitrite, ethyl chloride spray along the diaphragm, ether anesthesia or ether intramuscularly, gastric lavage and stellate ganglion block. In rare cases, unilateral phrenicectomy or phrenic nerve crush is required.

Penicillin: We administer this drug if pulmonary congestion or other signs of congestive failure are present or if the temperature is elevated, i.e., above 102° F.

Alcohol and Tobacco: Whiskey should not be given in acute coronary occlusion since it may increase the pulse rate. Smoking should be prohibited.

Cortisone and ACTH: Although these hormones have sometimes been found helpful experimentally, they are of no value clinically and may even be dangerous.

SUMMARY

The diagnosis of acute coronary occlusion has been facilitated and its treatment improved.

At the onset of the attack the electrocardiogram may be normal or show only slight changes.

The major therapeutic advances include oxygen administration, a low calorie diet, the judicious use of digitalis and quinidine, the avoidance of such drugs as Adrenalin and nitroglycerin, and the employment of anticoagulant and pressor drugs. Therapy must be individualized, particularly in reference to the time chair treatment is begun, the time of ambulation, and the time for returning to work.

The majority of patients can be treated at home.

The pain which ushers in the attack should be relieved immediately. For this purpose, morphine is most efficacious. Nitroglycerin is not effective, and may be dangerous.

The patient's anxiety must be allayed; he should be reassured that he, like the vast majority of patients, will make a good recovery and resume a full, productive life.

Indiscriminate prolonged bed-rest for all patients is inadvisable. The period of bed-rest is determined by the physical and psychic state of each patient. Some mild cases are permitted to be in a chair on the second or third day; others, after a week. Early chair treatment has definite advantages.

In the average mild case, the patient begins to walk during the fourth week.

The routine use of anticoagulants is unnecessary. They should be employed in patients with heart failure or shock, and in those who develop peripheral phlebitis, peripheral arterial embolism, or pulmonary embolism. When anticoagulants are administered, the patient should be under close supervision.

We believe that anticoagulants, administered during the premonitory phase of coronary thrombosis, are inefficacious; they neither prevent nor hasten the progress of the thrombosis.

Anticoagulants are contraindicated in patients with a history of bleeding tendency, ulcerative colitis, peptic ulcer, renal or hepatic disease, or a cerebrovascular accident.

It is important to differentiate coronary occlusion from non-specific pericarditis, since anticoagulants appear to be harmful in this condition.

The electrocardiogram should not be used as a criterion for determining the progress of the patient and the time when he may sit up, begin to walk, or return to work. Neither should undue reliance be placed upon the sedimentation rate as a guiding factor in treatment.

The treatment of heart failure in coronary occlusion is the same as if coronary occlusion were not present, but special care is necessary to prevent digitalis intoxication.

A low calorie diet is important, for it diminishes the work of the heart, prevents gastrocardiac reflexes, and reduces weight in the obese.

Constipation and distention must be prevented. Cold milk and fruit juices should be avoided and laxatives used.

Nausea and vomiting are benefited by the oral or intramuscular administration of anti-motion sickness drugs.

Early treatment of shock is essential. The vasopressor drugs are helpful, if administered early. If congestive failure is a factor, strophanthin or digitalis should be given.

Pulmonary edema requires immediate treatment with morphine. If necessary, aminophylline, strophanthin, mercurials, oxygen under pressure, and rotating tourniquets or phlebotomy are employed. The inhalation of alcohol vapor is occasionally efficacious.

Arrhythmias occur frequently and often remit. The indications for the treatment of each type are discussed and the details outlined. Quinidine is not used routinely.

Hiccough may be a serious problem. Reassurance of the patient is most important. Adequate sedation should be used. Numerous successful therapeutic measures are available.

Cortisone and ACTH are not efficacious in coronary occlusion.

Antibiotics are administered if pulmonary congestion or signs of congestive heart failure are present, or if the temperature is above 102° F.

Whiskey should not be given in acute coronary occlusion, since it may increase the pulse rate. Smoking should be prohibited.

The prognosis in coronary occlusion has greatly improved during the past 30 years. In private practice, the mortality rate during the first attack is now five per cent or less. Most patients can be rehabilitated within two or three months. The vast majority makes a fair or good recovery, more than half make an excellent functional recovery. Four out of five return to work.

RESUMEN

El diagnóstico de la oclusión coronaria aguda, se ha facilitado y su tratamiento ha mejorado.

Al principio del ataque el electrocardiograma puede ser normal o sólo mostrar ligeros cambios.

Los adelantos terapéuticos más importantes incluyen administración de oxígeno, alimentación baja en calorías, el uso juicioso de la digital y de la quinidina, el evitar drogas tales somo la adrenalina y la nitroglicerina y el empleo de drogas anticoagulantes y las que actúan sobre la presión. El tratamiento debe ser individualizado en particular en lo relativo al tiempo en que el enfermo puede ser colocado en silla; el tiempo de empezar la demabulación y el del regreso al trabajo.

La mayoría de los enfermos pueden tratarse a domicilio.

El dolor con que se inicia el ataque debe ser aliviado inmediatamente, para lo que la morfina es lo más eficaz. La nitroglicerina no es eficaz y puede ser peligrosa. La ansiedad del enfermo debe ser calmada; deben dársele seguridades de que él como la gran mayoría de los enfermos, tendrá una recuperación rápida y podrá volver a una vida completamente productiva.

No es aconsejable el prolongado reposo en cama sin distinciones.

El período de reposo en cama se determina por el estado psíquico y físico del enfermo en cada caso. Algunos casos moderados pueden permitirse el pasar a la silla en el segundo o tercer día; otros después de una semana. El pasarlos al reposo en sillón pronto puede tener ventajas definidas.

En el caso moderado medio, el enfermo empieza a caminar durante la cuarta semana.

El uso rutinario de los anticoagulantes no es necesario. Deben emplearse en enfermos con desfallecimiento cardiaco o shock y en los que presentan flebitis periférica, embolia arterial periférica, o embolia pulmonar. Cuando

se administran los anticoagulantes el enfermo debe estar bajo vigilancia estrecha.

Creemos que los anticoagulantes administrados durante la fase premonitoria de la trombosis coronaria son ineficaces; ni previenen ni apresuran la evolución de la trombosis.

Los anticoagulantes están contraindicados en los enfermos con antecedentes de tendencia hemorrágica, colitis ulcerosa, úlcera péptica, enfermedad renal o hepática, o accidente cerebrovascular.

Es importante diferenciar la oclusión coronaria de la pericarditis no específica ya que los anticoagulantes parecen ser dañosos en esta afección.

El electrocardiograma no debe usarse como criterio para determinar la evolución del enfermo y el tiempo cuando debe sentarse, empezar a caminar o regresar al trabajo. Tampoco debe tenerse demasiada confianza en la sedimentación globular como guía del tratamiento.

El tratamiento del desfallecimiento cardiaco en la oclusión coronaria es el mismo que si la oclusión no se tuviera presente pero debe tenerse especial cuidado en evitar la intoxicación digitálica.

Es importante la dieta baja en calorías porque disminuye el trabajo del corazón, evita los reflejos gastrocardiacos y reduce el peso de los obesos. Deben prevenirse la distensión y el estreñimiento.

La leche fría y los jugos de frutas deben evitarse y deben darse laxantes. La náusea y el vómito mejoran por el uso oral o intramuscular de medicamentos contra el mareo.

El tratamiento inmediato del shock es esencial. Las drogas vasopresoras son útiles si se administran pronto. Si hay el factor de insuficiencia congestiva deben darse estrofantina o digital.

El edema pulmonar debe tratarse con morfina. Si es necesario deben usarse la aminofilina, estrofantina, mercuriales, oxígeno a presión, torniquetes o flebotomía han de emplearse. La inhalación de vapores de alcohol es eficaz a veces.

Las arritmias se presentan a menudo y frecuentemente remiten. Las indicaciones para el tratamiento de cada forma se discuten y los detalles se proporcionan. La quinidina no se usa de manera rutinaria. El hipo puede ser un problema serio. El dar confianza al enfermo es lo más importante. Se usará sedación adecuada. Hay numerosas medidas terapéuticas.

La cortisona y la ACTH no son eficaces en la oclusión coronaria.

Se administrarán antibióticos si la congestión pulmonar o signos de insuficiencia congestiva se presentan o si la temperatura asciende arriba de 102 F.

No debe darse whisky en la oclusión aguda puesto que aumenta la frecuencia del pulso. Debe prohibirse fumar.

El pronóstico en la oclusión coronaria ha mejorado grandemente durante los últimos treinta años. En la práctica privada la mortalidad durante el primer ataque es de 5 por ciento a menos.

La mayoría de los enfermos pueden rehabilitarse dentro de dos o tres meses. La gran mayoría logran una recuperación bastante o buena; más

de la mitad la hacen excelente recuperación funcional. Cuatro de cada cinco, regresan al trabajo.

RESUME

Le diagnostic d'occlusion coronarienne aiguë se fait maintenant plus facilement et son traitement a été amélioré.

Au début de l'attaque, l'électrocardiogramme peut être normal, ou montrer seulement des altérations légères.

Les éléments thérapeutiques essentiels comprennent l'administration d'oxygène, un régime pauvre en calories, l'emploi judicieux de digitaline et de quinidine, le rejet de produits tels que l'adrénaline et la nitroglycérine, et l'utilisation de produits anticoagulants et de toniques vasculaires. Le traitement doit varier en fonction du malade, surtout en ce qui concerne le moment du lever, de la promenade, et de la reprise du travail.

La majorité des malades peut être traitée à domicile.

La douleur qui apparait lors de l'attaque devrait être soulagée immédiatement. Dans ce but, la morphine est le médicament le plus efficace. La nitroglycérine n'est guère active et peut être dangereuse.

L'anxiété du malade doit être calmée; on doit lui donner l'assurance que, comme la grande majorité des malades, il guérira lui-même et reprendra une vie pleine et productive.

Le repos prolongée au lit sans discrimination pour tous les malades n'est pas souhaitable. La période de repos intégral au lit est déterminée par l'état physique et psychique de chaque malade. On permet aux cas bénins de s'asseoir sur une chaise le second ou le troisième jour; dans les autres après une semaine. Le traitement consistant à faire lever précocément le malade a des avantages précis.

Dans le cas bénin moyen, le malade commence à marcher au cours de la quatrième semaine.

L'utilisation systématique de produits anticoagulants n'est pas indispensable. Ils devraient n'être employés que chez les malades atteints d'arrêt cardiaque ou de shock, et chez ceux chez lesquels se développe une phlébite périphérique, une embolie artérielle périphérique, ou une embolie pulmonaire. Quand les anticoagulants sont administrés, le malade doit être soumis à une étroite surveillance.

Nous estimons que les anticoagulants, administrés durant la phase prémonitoire de la thrombose coronarienne sont inefficaces; ils n'arrêtent ni ne hâtent le progrès de la thrombose.

Les anticoagulants sont contre-indiqués chez les malades qui ont tendance à l'hémorragie, à la colite ulcéreuse, à l'ulcère peptique, aux affections rénales ou hépatiques, ou à un accident cérébrovasculaire.

Il est important de différencier l'occlusion coronarienne de la péricardite non spécifique, depuis que l'on sait que les anticoagulants peuvent être nuisibles dans ce dernier cas.

L'électrocardiogramme ne devrait pas être utilisé comme critère pour déterminer le progrès du malade et le temps au bout duquel on peut l'autoriser à se lever, puis à marcher, puis à reprendre le travail. Pas plus

qu'on ne doit accorder une confiance excessive au taux de sédimentation comme facteur déterminant dans le traitement.

Le traitement de l'arrêt cardiaque dans l'occlusion coronarienne est le même que s'il n'esistait pas d'occlusion coronarienne, mais on doit faire très attention à empêcher l'intoxication par la digitaline.

Le régime pauvre en calories est important, car il diminue le travail du coeur, empêche les réflexes gastro-cardiaques, et réduit le poids chez les obèses.

La constipation et la distension colique doivent être évitées. Il faut proscrire le lait froid et les jus de fruits et on peut utiliser les laxatifs.

La nausée et les vomissements sont améliorés par l'administration des produits par voie buccale ou intramusculaire.

Le traitement précoce du shock est capital. Les toniques vasculaires sont utiles, s'ils sont administrés précocément. S'il existe un élément de congestion par insuffisance cardiaque, la strophantine ou la digitaline doivent être prescrites.

L'oedème pulmonaire demande un traitement immédiat par la morphine. Si nécessaire, l'aminophylline, la strophantine, les produits mercuriels, l'oxygène sous pression et la saignée par phlébotomie doivent être utilisés. L'inhalation de vapeur d'alcool est éventuellement efficace.

L'arythmie survient fréquemment et souvent finit par disparaitre. Les indications du traitement des malades de ce type sont discutées et les détails suggérés. La quinidine n'est pas utilisée d'une façon systématique.

Le hoquet peut être un problème grave. Le fait de rassurer le malade est le plus important. On devrait utiliser des médications qui apportent la sédation immédiate. On dispose de nombreux moyens de traitement satisfaisants.

La cortisone et l'A.C.T.H. ne sont pas efficaces dans l'occlusion coronarienne.

Les antibiotiques sont administrés s'il existe une congestion pulmonaire, ou des signes d'insuffisance cardiaque congestive, ou si la température est au-dessus de 39°.

On ne devrait pas autoriser la boisson de whisky dans l'occlusion coronarienne aiguë, car il peut en résulter une augmentation du pouls. L'usage des cigarettes doit être interdit.

Le pronostic de l'occlusion coronarienne a été grandement amélioré ces trente dernières années. En pratique privée, le taux de mortalité durant la première attaque est maintenant de 5% ou moins. La plupart des malades peuvent être rendus à la vie active en deux à trois mois. La grande majorité d'entre eux peut avoir une guérison moyenne ou bonne, plus de la moitié peut retrouver un état fonctionnel excellent. Les 4/5 peuvent reprendre leur travail.

ZUSAMMENFASSUNG

Die Diagnose des akuten Koronar-Verschlusses ist erleichtert und seine Behandlung verbessert worden.

Zu Beginn de anfalls kann das Elektrocardiogramm normal sein oder nur leichte Veränderungen zeigen.

Die hauptsächlichen therapeutischen Fortschritte umfassen Sauerstoff-Handhabung, eine calorienarme Diät, die vorsichtige Verwendung von Digitalis und Chinidin, das Vermeiden von Mitteln wie Adrenalin und Nitroglyzerin und den Einsatz von Antikoagulantien und blutdrucksteigernden Mitteln. Die Behandlung muss dem Einzelfall angepasst sein, besonders im Hinblick auf den Zeitpunkt, an dem mit dem Aufstehen begonnen wird, den Zeitpunkt des Überganges in ambulante Behandlung und dem der Rückkehr an die Arbeit.

Die Mehrzahl der Patienten kann zu Hause behandelt werden.

Der Schmerz, der den Anfall ankündigt, soll auf der Stelle behoben werden. Für diesen Zweck ist das Morphium am meisten wirksam. Nitroglyzerin wirkt nicht und kann gefährlich sein.

Dem Angstgefühl des Patienten muss Erleichterung verschafft werden. Man soll ihm fest versichern, dass er sich, wie der grösste Teil solcher Kranken, gut erholen und seine volle produktive Tätigkeit wird wieder aufnehmen können.

Unterschiedslose überlange Bettruhe für alle Patienten ist nicht ratsam. Die Zeitspanne der Bettruhe wird bestimmt durch die physische und psychische Verfassung eines jeden Kranken. Gelegentlich kann man in leichten Fällen erlauben, am 2. oder 3. Tage im Stuhl zu sitzen; bei anderen ist dies nach einer Woche möglich. Eine frühzeitige Einbeziehung des Sitzens in der Behandlung hat bestimmte Vorzüge.

In einem durchschnittlich leichten Fall beginnt der Kranke während der 4. Woche mit Spaziergängen.

Die systematische Verwendung von Antikoagulantien ist unnötig. Sie käme in Betracht bei Patienten mit Versagen des Herzens oder mit Schock und bei solchen, bei denen sich eine periphere Phlebitis, periphere arterielle Embolie oder eine Lungenembolie einstellt. Wenn aber Antikoagulantien verabfolgt werden, dann muss der Patient sorgfältig überwacht werden.

Wir sind der Ansicht, dass Antikoagulantien wirkungslos sind, wenn sie während der Prodromal-Phase der Koronar-Thrombose gegeben werden; weder verhindern sie, noch beschleunigen sie das Fortschreiten der Thrombose.

Antikoagulantien sind kontraindiziert bei Patienten mit anamnestischen Angaben über Blutungsbereitschaft, Colitis ulcerosa, Magengeschwür, Nierenoder Lebererkrankung oder einer Schädigung der Hirngefässe.

Von Wichtigkeit ist es, einen Koronar-Verschluss abzugrenzen von einer unspezifischen Pericarditis, de bei diesem Zustandsbild Antikoagulantien schädlich erscheinen.

Das Elektrocardiogramm sollte nicht als ein Kriterium dienen zur Bestimmung der Besserung des Befundes des Patienten und des Zeitpunktes an dem er aufsitzen, mit Spaziergängen beginnen, oder an seine Arbeit zurückkehren kann. Ebenso wenig sollte übermässiges Vertrauen auf die Blutsenkungsgeschwindigkeit gesetzt werden, als einem leitenden Faktor in der Behandlung.

Die Behandlung des Versagens des Herzens beim Koronar-Verschluss bleibt die gleiche wie wenn ein Koronar-Verschluss nicht bestünde, jedoch

ist besondere Vorsorge notwendig, um eine Digitalis-Vergiftung zu verhindern.

Eine kalorienarme Diät ist wichtig, denn sie verringert die Herzarbeit, verhindert gastro-cardiale Reflexe und vermindert das Gewicht bei Fettleibigkeit.

Verstopfung und Blähungen müssen vermieden werden. Kalte Milch und Fruchtsäfte sollten vermieden und von Abführmitteln Gebrauch gemacht werden.

Gegen übelkeit und Erbrechen geht man mit oralen oder intramuskulären Gaben von Mitteln gegen Bewegungskrankheiten vor.

Frühzeitige Behandlung des Schocks ist wesentlich. Die Blutdruck steigern den Mittel sind eine gute Hilfe, wenn sie frühzeitig gegeben werden. Spielt ein Schlaganfall eine Rolle, soll Strophantin oder Digitalis gegeben werden.

Ein Lungenoedem erfordert sofortige Behandlung mit Morphium. Falls notwendig, sind Aminophyllin, Strophantin, Quecksilberpräparate, Sauerstoff unter Druck und Staubinden oder Aderlasse zu verwenden. Die Inhalation von Alkoholdämpfen ist gelegentlich wirkungsvoll.

Arrythmien kommen häufig vor und verschwinden oft. Die Indikationen zur Behandlung einer jeden Krankheitsform werden besprochen und die Einzelheiten dargestellt. Chinidin wird nicht gewohnheitsgemäss gebraucht.

Singultus kann ein ernsthaftes Problem sein. Beschwichtigung des Patienten ist besonders wichtig. Entsprechende Beruhigungsmassnahmen müssen angewandt werden. Zahlreiche, gut wirksame therapeutische Massnahmen stehen zur Verfügung.

Kortison und ACTH haben keine Wirkung beib Koronar-Verschluss.

Antibiotika gebraucht man, falle eine Lungenstauung oder Zeichen eines Herzversagens durch Stauung vorliegen oder die Temperatur über 39° anzeigt.

Whisky sollte beim akuten Konorar-Verschluss nicht gegeben werden, weil dadurch eine Pulsbeschleunigung zustande kommen kann. Das Rauchen muss verboten werden.

Die Prognose des Konorar-Verschlusses hat sich im Laufe der vergangenen 30 Jahre erheblich gebessert. In der Privatpraxis beträgt die Sterblichkeitsziffer während der ersten Attacke jetzt 5% oder weniger. Die meisten Patienten können innerhalb von 2 oder 3 Monaten genesen. Der grösste Teil erholt sich leidlich oder gut, mehr als die Hälfte erholt sich funktionnel ausgebeichnet. 4 von 5 nahmen ihre Arbeit wieder auf.

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Cough Hazard

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The high individual incidence, the ubiquitous occurrence and common prevalence of cough are not an index of its potentially dangerous implications. Assaying the causes, sources and mechanism of cough reveals the manifold liability of physiologic sequence of events the manifestations of which are recognized as cough.

Sensory receptors through which cough is initiated are the nerve endings of the vagus and the glossopharyngeal nerve. Their extensive ramifications cover, directly or through communicating branches, all parts of the respiratory tract, also, some of the organs below the diaphragm and through anastomosis, the external ear canal and the ear drum. Physical, mechanical, chemical, thermal, allergic, toxic and microbial agents may provoke stimuli which activate trigger points and result in cough. The latter may be induced by a gamut of changes from respiratory infection to bronchial asthma, from foreign bodies to tumors, from pleural involvement to cardiovascular disease and other pathologic conditions.

Clinically, cough is a variable, abrupt expiratory thrust of air from the lung, associated with phonation. It interrupts the normal pattern of respiration. Its character is influenced by the laryngeal structures, the competence of laryngeal innervation, by the localization, type and extent of disease which provokes it, the status of the respiratory muscles, by the age of the patient and the general physical condition of the body. During cough, the chest serves as a rigid-walled compression chamber. Compressed air is the medium of expulsive force which aims at the removal of accumulated exudate, transudate, aspirated foreign body or extravasated blood from the air passageways. Compression of air in the lung is brought about by a forceful expiratory effort while the glottis is closed. The closure of the latter is secured by the coordinated function of the adductor and tensor muscles of the larynx. These are the lateral crico-arytenoid, the transverse and oblique arytenoids, the internal and external thyro-arytenoid and cricothyroid muscles. The capacity with which this group of small muscles is able to resist the high pressure of compressed air in the lower air passages is astounding. During strenuous cough the intrapulmonary pressure may reach as high as 200 mm. of mercury over and above atmospheric pressure. This is accomplished by contraction of the expiratory muscles, the abdominal rectus, the external and internal oblique and transversus muscles of the abdomen. The lower ribs are fixed by the internal intercostal, the lower serratus posterior and abdominal muscles, thus assuring satisfactory descent of the diaphragm during its inspiratory contraction. During the compressive phase of cough,

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the diaphragm is in a state of intense contraction. In this manner the base of the thoracic cavity is changed from a soft, flexible musculotendinous partition into a firm structure the rigidity of which is comparable to that of the bony thoracic cage.

At the moment the glottis opens, the forceful contraction of the thoracic and abdominal expiratory muscles results in an abrupt decrease in the intrapulmonary pressure while the previously compressed mass of air leaves the respiratory tract with great velocity. The serious implications of the loss of diaphragmatic function in certain diseases, particularly in so-called hypertrophic emphysema cannot be appreciated unless one is aware of the triple role of the diaphragm in the cough mechanism. 1. Its descent is responsible for from 37 to 47 per cent of air taken into the lung during quiet inspiration. 2. It resists elevated intrapulmonary and intra-abdominal pressures during the compressive phase of cough. 3. It relaxes simultaneously with the sudden opening of the glottis during the expulsive phase of cough and serves like a rapidly moving piston which transmits the increased intra-abdominal pressure to the lung. According to Weber, kymograms of the chest taken during cough revealed wide excursions of the diaphragm. The lowest position of the latter coincided with the end of deep inspiration directly preceding cough. The highest position of the diaphragm, at the level of the caudal pole of the hilum, corresponds to the completion of cough. The excursions of the diaphragm were found from three to four times wider during cough than during normal respiration.

When the effort and energy required by cough are conducive to satisfactory removal of material from the air passageways, cough is considered adequate. In a great many instances, however, one can observe tussive insufficiency or tussive failure. In tussive insufficiency the cough effort is incapable of dislodging and removing inflammatory exudates or other substances from the respiratory tract. This, in turn, is likely to be followed by recurrent coughing spells of varying intensity. In this category belong patients with bronchopulmonary affections associated with the formation of tenacious, sticky inflammatory products adherent to the walls of the respiratory passages. Tussive failure is observed in individuals whose cough is caused by tumors of the lung, mediastinum and the organs it contains, aneurysm or pathologic changes of the pleura, the diaphragm and other structures along the entire course of the respiratory tract, which exert pressure upon the sensory nerve receptors. The cough in these cases serves no useful purpose physiologically although it may call attention to the underlying disease.

Tussive insufficiency and tussive failure, regardless of their origin, are always a liability because of the stress and strain associated with coughing and also, because of immediate untoward consequences.

The following table represents a list of the most important harmful sequelae of inadequate cough (tussive insufficiency and tussive failure).

1. Interference with the healing of inflammatory diseases of the bronchi and lung parenchyma.

2. Interference with the patient's rest.
3. Rise in temperature.
4. Dyspnea.
5. Exhaustion.
6. Headache.
7. Subconjunctival hemorrhage.
8. Insomnia.
9. Loss of appetite.
10. Vomiting.
11. Urinary incontinence.
12. Postoperative disruption of wounds of the anterior abdominal wall.
13. Pain in the chest.
14. Fracture of ribs.
15. Possible droplet spread of infection from one part of the lung to another or from a lung to the opposite side.
16. Pulmonary hemorrhage.
17. Bronchiectasis.
18. Bronchospasm.
19. Lowering of the threshold of cough irritability.
20. Mediastinal emphysema. (Pneumomediastinum).
21. Spontaneous pneumothorax.
22. Subcutaneous emphysema.
23. Cervical hernia.
24. So-called hypertrophic emphysema.
25. Strain on the right ventricle of the heart.
26. Tussive syncope or its formes frustes.

We wish to give a brief elucidation of some of these items. Pain in the chest during cough may be attributable to actual pleurisy, trauma to costochondral cartilages (Tietze's syndrome), pathologic affections of other structures of the chest wall or to muscular hypoxia of the intercostal muscles or diaphragm (diaphragmatic angina).

Bronchial and bronchiolar walls weakened and damaged by severe or chronic inflammation of any etiology are sites of lessened resistance in relation to increased intrapulmonary pressure. These areas of the lower respiratory tract may become dilated and deformed under impact of pneumatic pulmonary hypertension during the compressive phase of cough. Undoubtedly, bronchial blockage with consequent atelectasis, superimposed parenchymal and bronchial infection and fibrosis contribute to the development of bronchiectasis in patients with long standing tussive insufficiency.

Bronchospasm is a functional abnormality the frequency of which is far greater than it is generally realized. It occurs not only in bronchial asthma and as the result of inhalation of irritating fumes, gases and dusts or aspiration of foreign bodies but also in patients with pulmonary fibrosis, congestion, and edema and in those with parenchymal infection or bronchial disease, bacterial, viral, rickettsial, protozoan or parasitic in origin. Pulmonary hypoxia resulting from excessive cough may lead to bronchospasm. Also, stretching of the bronchial mucosa during strenu-

ous coughing may irritate the vagus sufficiently so as to produce a substance at its terminal points, which is chemically identical with acetylcholine. The latter may cause spasm of the peribronchial and peribronchiolar smooth muscles. Muscular spasm of this type, particularly in the presence of mucosal edema or fibrosis of the respective air passages and also, when there is accumulation of inflammatory exudate or other material within the lumen, interferes with spontaneous bronchocatharsis. It obviates normal bronchial peristalsis and it is likely to increase bronchial secretions and thus enhance the possibility of occlusive alterations.

Hypoxia which may result from interference with normal pulmonary ventilation during severe coughing spells is bound to increase the irritability of the nerve endings of the vagus and be followed by more cough induced by "subliminal" provocation. Herein lies the foundation of the axiom, cough begets cough.

In 1888, Mueller first offered a plausible explanation of the origin of mediastinal emphysema (pneumomediastinum). According to his thesis, under the stress and strain of severe coughing, intrapulmonary air may disrupt some of the alveoli. From the latter, air escapes into the adjacent interstitial tissue. From here, bubbles of air pass to the hilum through the connective tissue which surrounds the bronchi and blood vessels. At the hilum the air enters the mediastinum. In other instances, air bubbles may find their way to the visceral pleura and thence subpleurally to the mediastinum. The painstaking studies of Macklin brought about experimental proof of the correctness of this assumption. He demonstrated that when air was blown into a region of the lung under pressure varying from 10 to 220 mm. of mercury, alveolar walls overlying the pulmonary vessels were distended. The floors of these alveoli developed many small ruptures. The invading air distends the loose connective tissue of the vascular sheaths as they converge and accumulate at the hilar region. Rasmussen and Adams found that cyclically induced sudden pressure of 30 to 35 mm. mercury at the carina was capable of producing interstitial emphysema of the lung in experimental animals. Joannides and Tsoulos produced interstitial emphysema of the lung by applying sustained elevated intrapulmonic pressure of 60 mm. of mercury.

Normally the alveoli are capable of withstanding increased intrapulmonary pressure without harm. Rupture in their perivascular wall may occur, however, during severe cough in patients with constitutional inferiority of the alveoli. Similar predisposition exists in cases where the structural integrity of air sacs is impaired by inflammatory changes. Severe bronchitis of diverse etiology, lobar pneumonia, bronchopneumonia, lung abscess, influenza, measles, diphtheria and whooping cough may be complicated by mediastinal emphysema. The occurrence of this condition in more than one member of the same family speaks in favor of hereditary predisposition. Complications of mediastinal emphysema include spontaneous pneumothorax, subcutaneous emphysema of the neck, chest, arms or the entire body, pneumoretroperitoneum, pneumoperitoneum, circulatory and respiratory embarrassment.

As a rule, the onset of symptoms is sudden, with sharp, stabbing knife-like pain. The pain is precordial or it is localized in the lower part of the chest near the sternum, rarely in the back or in the interscapular region. Anterior chest pain may radiate to the neck, shoulder, down the arms, to the back or between the scapulae. The pain is likely to be aggravated on deep breathing, coughing, swallowing, moving the head or sudden change in position. Pain is attributed to distention of mediastinal tissues. It lasts from few minutes to few hours or several days. At times the appearance of pain is gradual and it is preceded by heaviness and pressure sensation in the chest. The latter is presumably due to interstitial emphysema of the lung. Abdominal pain is complained of when pneumoretroperitoneum develops. In less than ten per cent of the cases, pain is absent.

Appearance and degree of dyspnea and cyanosis are predicated upon the amount of air collecting in the mediastinum. When the pressure of the latter is high, it interferes with the blood flow to and from the heart and may lead to circulatory crisis. Macklin refers to this condition as "mediastinal air block." Co-existent compression of the lung parenchyma by pulmonary interstitial emphysema may cause bloating and stiffening of the lung and its virtual immobilization in the inspiratory position, thus resulting in respiratory distress.

Spontaneous pneumothorax is found in about 50 per cent of these cases and subcutaneous emphysema in about 25 per cent.

Although it is known that protracted lung infections, widespread bronchospasm and pulmonary fibrosis play a role in the pathogenesis of so-called hypertrophic emphysema, chronic, excessive cough should be recognized as the principal factor in the etiology of this disease. The degree of pulmonary pneumatic hypertension during cough depends upon the force exerted by the expiratory muscles and upon the integrity of other pertinent components of the respiratory tract and the ventilatory mechanism. Cough as a reflex mechanism is a useful defense reaction of the body; nevertheless, even under the best of circumstances it represents undue stretch and strain upon the alveoli and the elastic elements of the lung. When this aerodynamic trauma is intense, frequent and protracted enough, its detrimental effect is inevitable. The deleterious influence of pneumatic alveolar hypertension which prevails in the lung during the compressive phase of cough can be more readily appreciated if the following changes are borne in mind. (1) Air currents are subject to the same physical laws as water currents. They move from a site of higher pressure toward areas of lower pressure. While during quiet respiration the intra-alveolar pressure cannot be higher than the atmospheric pressure which prevails in the bronchi, during the compressive phase of strenuous coughing the intra-alveolar pressure may rise to 200 mm. of mercury over and above atmospheric pressure. (2) The physical law of communicating vessels applies to the relationship between respiratory bronchioles and their respective cluster of alveoli. The same pressure which exists in the narrow respiratory bronchiole is transmitted undiminished to the

entire perimetry of all of the respective alveoli. (3) In the presence of bronchial constriction the effect of traumatizing pneumatic hypertension is cumulative. With each coughing spell an increment of positive pressure is added to that of air entrapped in the corresponding alveoli. The resulting sustained, excessive intra-alveolar hypertension culminates in rupture of the alveolar septa. (4) At the termination of the compressive phase of cough, when there is a precipitous drop in the intrapulmonary pressure, evacuation of the air is slower from alveoli attached to spastic, partially occluded bronchi than from alveoli connected to bronchi of normal lumen. This exerts an appreciable distending influence upon the alveoli implicated. This phenomenon may be referred to as regional expiratory lag. It is our opinion that the existence of such stenotic areas in some of the smaller bronchi explains the seemingly haphazard and bizarre topography of pulmonary bullae and subpleural blebs.

Destruction of a great many of the alveoli and much of the elastic elements of the lung inexorably follows chronic, severe, uncontrolled cough. The harmful influence of cough upon these structures depends not only upon the severity of cough but also upon the pathologic conditions which are the incentive causes of cough and also upon the age of the patient. When as a consequence of infection the vitality of the lung tissue is impaired, or because of diminished blood flow through fibrosed vessels the nutrition of these tissues is below par, they become more vulnerable to the destructive force of tussive aerodynamic trauma. In general, tensile strength and resilience of the tissues are less in senescence than in young individuals. The more advanced the age the greater the possibility of damage by pulmonary pneumatic hypertension.

In reference to chronic lung infection and protracted cough, undoubtedly, the origin of so-called hypertrophic emphysema, ordinarily encountered in older persons, is traceable to early years of life in a great many instances. Chronic infectious diseases of childhood, with associated pulmonary fibrosis and possible bronchiectasis, are potent agents in initiating pathologic sequels the ultimate result of which is emphysema. Long-standing allergic bronchial asthma may have an identical influence. Oftentimes infections of this type heal after a prolonged course. Patients with emphysema who seek medical attention may completely forget about them. But there remain destructive alterations in the lung tissue. It may seem paradoxical that, in the presence of such lung changes, no manifest emphysema is evident during the early years of life. The reason for the absence of symptoms of emphysema in these young persons is that the elastic fibers of the lung, which remained intact, continue to function with a capacity sufficient to maintain the normal respiratory motions of the lung. Subjective and objective manifestations of emphysema become obvious, however, when these individuals reach old age. At this time the previously intact elastic fibers either undergo senile degeneration or are damaged by intercurrent lung infections or by bouts of severe coughing.

The last item we wish to discuss in some detail is tussive syncope. Loss of consciousness following severe coughing spells was first recorded in

the medical literature by Charcot in 1876. Usually young or middle-aged adults are affected, individuals who are suffering from laryngitis, bronchitis, whooping cough, chronic pulmonary infections, fibrosis or so-called hypertrophic emphysema. Premonitory symptoms include laryngeal irritation, tickling in the upper air passages and giddiness. Attacks of unconsciousness occur during violent coughing paroxysms regardless of the position of the patient. In some cases, however, syncopal attacks with coughing are encountered only when the patient is in the upright position. Duration of the unconsciousness varies from few seconds to two-three minutes. The patient collapses and may hurt himself when slumping to the floor. These episodes may be associated with convulsive, epileptiform movements of the arms and legs and occasionally, with urinary incontinence. Subsequently, mental confusion may be noted. For the sake of diagnostic accuracy, it is well to keep in mind the formes frustes of this condition. These are characterized by dizziness, transient light-headedness, brief periods of confusion, tingling sensation in the hands and feet and paresthesias in the head and trunk. Prior to minor or major attacks the patient's face becomes congested and he is in an obviously disturbing state of hypoxia.

As to the causation and mechanism of tussive syncope, a number of concepts have been offered. Charcot referred to it as laryngeal vertigo. Others proposed the term, laryngeal epilepsy. Recent investigations prove that genuine epilepsy is not a factor in its etiology. The experimental observations of Wilkins and Friedland point the way toward the understanding of this clinical entity. They reported loss of consciousness in normal persons during Valsalva experiment (forced expiration against closed glottis). Also, Rook observed that some of the young men taking physical fitness tests for service in the Royal Air Force lost consciousness at the end of forced expiration while blowing a column of mercury contained in a U tube to a height of 40 mm. and holding it there as long as possible.

McCann and his associates studied the problem of tussive syncope with meticulous precision. In one of their patients, syncope and convulsions were produced by the Valsalva maneuver with the patient in the recumbent position. Cinefluorograms taken during paroxysmal coughing revealed bulging of the right atrium of the heart, the venae cavae and the pulmonary segment. Also, on fluoroscopy, they observed trapping of the blood within the pulmonary circulation during paroxysmal coughing. Their data found on cardiac catheterization are of utmost interest. During a paroxysm of coughing the pressure in the right ventricle increased to 30 mm. of mercury. During quiet breathing, right intraventricular pressures were: on inspiration, systolic 41, diastolic five, on expiration, systolic 18 mm. of mercury, diastolic 0. The increase in the right intraventricular pressure was associated with a pronounced decrease in the systemic arterial pressure, namely, 60 mm. of mercury systolic and 50 diastolic. These observations support the idea that tussive syncope is caused by congestion of the cerebral veins, by decreased cardiac output

and hypoxemia. We are of the opinion that another factor may have a contributory role in this respect. Excessive intrapulmonary pressure during a severe coughing spell may exert irritation upon the broncho-mucosal nerve endings of the vagus to such an extent that it may activate a vago-cortical reflex. This, in turn, results in loss of consciousness and other manifestations of this syndrome.

CONCLUSIONS

1. The asessment of cough can be made only in the light of its possible advantages and harmful implications.

2. Cough should be considered a useful reflex which, however, does not always serve its innate purpose.

3. For the sake of its successful management it is mandatory that distinction be made between adequate cough, tussive insufficiency and tussive failure.

4. The untoward consequences of cough depend upon its intensity, frequency and duration.

5. When cough persists for an extended period of time after clearing of a respiratory infection, the damaging effect of cough continues too.

6. The manifold hazards of cough are enumerated in the text and some of its adverse influences have been critically analyzed.

7. Irreparable harm may result from underestimating or misinterpreting the significance of cough.

8. Obviously, there is an urgent need for greater awareness of the potential damage of cough so as to accomplish its satisfactory treatment as well as to prevent its serious sequelae.

CONCLUSIONES

1. La estimación de la importancia de las tos sólo se puede hacer teniendo en cuenta sus ventajas posibles y sus consecuencias.

2. La tos debe considerarse un reflejo útil que no siempre sirve a su objetivo.

3. A fin de obtener un tratamiento eficaz es indispensable que se establezca una distinción entre la tos adecuada, insuficiencia tusígena y tos deficiente.

4. Las consecuencias indeseables de la tos dependen de su intensidad, frecuencia y duración.

5. Cuando la tos persiste por un período de tiempo que sobrepasa la mejoría de la infección respiratoria, los efectos dañinos de la tos también se continúan.

6. Los múltiples riesgos de la tos se enumeran en el texto y algunas de sus influencias perjudiciales se analizan críticamente.

7. Puede resultar daño irreparable por no estimarse con justeza su significación.

8. Es evidente que se requiere mayor atención a la posibidad de que la tos produzca daños si se quiere llegar a un tratamiento satisfactorio y evitar serias consecuencias.

RESUME

1. La sédation de la toux ne doit être envisagée qu'après avoir pesé les avantages et les complications qui pourraient en résulter.

2. La toux devrait être considérée comme un réflexe utile, et qui cependant ne sert pas toujours son but essentiel.

3. Pour la réussite de cette opération, il est absolument nécessaire que soit établie la distinction entre toux efficace, toux insuffisante et toux complètement absente.

4. Les inconvénients qui peuvent résulter de la toux dépendent de son intensité, de sa fréquence et de sa durée.

5. Lorsque la toux persiste pendant une période étendue après la disparition de l'infection respiratoire, les inconvénients qui en résultent persistent en même temps.

6. Les différents dangers de la toux sont énumérés dans le texte, et certaines de ses fâcheuses conséquences ont été l'objet d'une analyse critique.

7. La sous-estimation ou la mauvaise interprétation de la valeur de la toux peuvent entrainer un mal irréparable.

8. Il y a évidemment une nécessité urgente à prêter une plus grande attention aux inconvénients possibles de la toux, comme d'en assurer le traitement satisfaisant aussi bien que d'en éviter les séquelles sérieuses.

SCHLUSSFOLGERUNGEN

1. Der Husten kann nur hinsichtlich seiner möglichen Vorteile oder schädlichen Folgeerscheinungen beurteilt werden.

2. Der Husten ist als ein nützlicher Reflex zu betrachten, der jedoch nicht immer seinem ursprünglichen Zweck dient.

3. Zur erfolgreichen Lenkung des Hustens ist es notwendig, zwischen adaequatem Husten, unzulänglichem und mangelhaftem Husten zu unterscheiden.

4. Die ungünstigen Folgen des Hustens hängen von seiner Intensität, Häufigkeit und Dauer ab.

5. Wenn der Husten längere Zeit nach Beseitigung der Infekte des Respirationstraktes fortdauert, hält die schädliche Wirkung des Hustens an.

6. Die vielfachen Schädlichkeiten des Hustens sind im Text aufgeführt, und einige seiner schädlichen Wirkungen wurden einer kritischen Betrachtung unterzogen.

7. Durch Unterschätzen oder Missdeutung der Hustenwirkung kann irreparabler Schaden entstehen.

8. Eine grossere Kenntnis der Schädigungsmöglichkeiten von Seiten des Hustens ist dringend erforderlich, um eine befriedigende Behandlung zu gewährleisten und schädliche Folgen zu verhüten.

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Cardiac Catheterization in Congenital Heart Diseases*

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Cardiac catheterization was done for the first time 25 years ago by Forssman,[1] who performed the maneuver on himself. However, this procedure was employed in the study and diagnosis of heart disease only after Cournand and Ranges[2] demonstrated the value and safety of the method in 1941. The method was subsequently completed by the addition of several collateral techniques. The most useful application of cardiac catheterization is in the diagnosis and study of congenital heart diseases.

Method and Technique

The patient should be admitted to the hospital one day before cardiac catheterization. If any evidence of infection or heart failure is found or if there are arrhythmias, the test is postponed until recovery. The patient is again kept under observation in the hospital for 24 hours following the test. Antibiotics are given before and after the procedure. Except for this, no other premedication is required for adults. Anesthesia or sedatives are sometimes needed in children, even though it is common experience[3] that an intelligent and gentle nurse can obtain more cooperation than a large dose of sedatives.

A 100 cm. long radio-opaque catheter is introduced through the median basilic vein of the left or right arm (saphenous vein in children under 5 years of age) which had been previously exposing it by a small incision through the skin, under local anesthesia. Then it can be advanced gently under fluoroscopic control, through the innominate vein, superior vena cava, right atrium, right ventricle, and pulmonary artery. The catheter can subsequently be advanced within the pulmonary artery until a small branch is blocked. Thus, pressures from the venous side of the pulmonary circulation can be measured (so called pulmonary capillary pressure.[4]) Then, while the catheter is pulled back, pressure readings and blood samples are taken in rapid succession from the right, left and main pulmonary artery, from the right ventricle and right atrium, from the inferior and superior vena cava and from any unusual structure which may be entered. Simultaneously with blood samples from the catheter, arterial blood samples from an indwelling needle introduced into the brachial or femoral artery, may be obtained during the procedure.

Measurement of oxygen consumption while blood samples are simultaneously obtained from the pulmonary artery and a systemic artery, makes possible the determination of cardiac output per minute through

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the use of Fick's principle. The following formula is then employed.[5]

$$1.\ \text{Cardiac output (ml. per min.)} = \frac{O^2 \text{ intake (ml. per min.)}}{O^2 \text{ content of arterial blood (vol. per cent)} - O^2 \text{ content of mixed venous blood (vol. per cent).}} \times 100$$

The same principle has been widely applied for the calculation of left-to-right shunts (septal defects or patent ductus arteriosus). It must be pointed out that there are many causes of errors in the measure of this shunt, so that the data sometimes differ from the results of autopsy or surgery.

Three different kinds of data are obtained during the procedure by observing:

(a) position of catheter;
(b) pressure tracings; and
(c) oxygen content of blood samples.

The position of the catheter cannot be determined with certainty by fluoroscopy alone. In particular, it is impossible to determine on which side of a valve the catheter tip lies. As each cardiac chamber or vessel has characteristic pressure patterns, pressure tracings are helpful in order to ascertain the location of the tip of the catheter, whenever a blood sample is obtained.

An abnormal position of the catheter, when its location is precisely ascertained, is the most important information which can be obtained by cardiac catheterization; the catheter may be passed through or into a patent ductus arteriosus, an aortic septal defect, a ventricular septal defect, an overriding or transposed aorta, an atrial septal defect, an anomalous pulmonary vein or a left superior vena cava.

Cardiovascular pressures may be measured with reasonable accuracy by means of a strain gage, an electromanometer, or an optical manometer connected with the catheter. However, the motion of the catheter by the heart beat may cause a severe distortion of the pressure pulses, thus somewhat invalidating an otherwise promising aspect of this study.

The following figures of pressure can be considered normal from a survey of the literature:[6]

	Systolic (mm. Hg.)	Diastolic (mm. Hg.)	Mean (mm. Hg.)
Right atrium			from —2 to +5
Right ventricle	from 17 to 31.5	from —0.5 to +7 (end of diastole)	
Pulmonary artery	from 11 to 29	from 4 to 13	from 8 to 19
Pulmonary "capillaries"			from 5 to 13

No significant gradient of systolic pressure exists normally between right ventricle and pulmonary artery.* On the other hand, the systolic pressure of the right atrium is about the same as the right ventricular

*It has been stated that a dilatation of the pulmonary artery may cause a moderate drop of the systolic pressure creating a gradient of 15 to 20 mm. Hg.

diastolic pressure. It is called, therefore, right atrial filling pressure.

Each organ consumes a different amount of oxygen. The blood which comes from the kidney, for instance, is rich in oxygen. The blood from the liver is poor in oxygen while that from the coronary sinus is the poorest of all. The venous blood of the right atrium is therefore a mixture of various venous bloods having different oxygen saturations. When the blood coming from a collateral vein enters the inferior vena cava, it does not mix well and has a tendency to form laminar flow. This may persist through the atrium and even within the right ventricle, so that the pulmonary arterial blood is often the only truly mixed blood. On account of this, the oxygen content of blood samples varies from chamber to chamber and even within the same chamber. Variations as great as 2.3[7] have been found in a couple of samples taken from the right atrium without moving the catheter.

The following differences in oxygen content are generally accepted as representing the maximum limits of normal. Superior vena cava and inferior vena cava usually show a difference of from 0 to 2 vol. per cent. Therefore, a gradient of at least 2 volumes per cent between the blood of the vena cava and that of the right atrium is necessary in order to determine the existence of a left-to-right shunt in the right atrium. However, if the samples of the two cavae are approximately the same and there is a difference in oxygen content between them and the right atrium of 1.5, this may be considered as indicative of left-to-right shunt, especially if there is clinical evidence supporting this diagnosis. Similarly, a difference greater than 0.9 vol. per cent between right ventricle and right atrium indicates either a left-to-right shunt between the ventricles or regurgitation of highly oxygenated blood from the pulmonary artery. On the other hand, the existence of a step-up in oxygen content in the pulmonary artery should not be considered as definite proof of the presence of patent ductus arteriosus because oxygenated blood from the left ventricle may be shunted directly across the defect and the pulmonary valve to the pulmonary artery in cases of high ventricular septal defect.

Failure to catheterize the pulmonary artery cannot be considered as evidence of pulmonic stenosis or atresia; unsuccessful attempts to pass the catheter through a clinically suspected septal defect or ductus arteriosus does not rule out its presence.

The pressures in the left side of the heart are normally higher than in the right side. Whenever there is an abnormal communication between the two sides, a left-to-right shunt occurs. Later on, pulmonary hypertension may develop. It usually causes an increase of pressure in the right ventricle and right atrium which may overcome the physiological difference and reverse the shunt causing cyanosis. If there is pulmonic stenosis associated with a septal defect, the pressure in the right heart is high since birth, and cyanosis may be present shortly afterwards. The same is true when the aorta is dextroposed.

Clinical Conditions Requiring Catheterization

Partial anomalous venous connection.—This malformation consists of the draining of one or more pulmonary veins into the right side of the heart. The most common sites are the superior vena cava, the right atrium, and the left innominate vein.[8] When the pulmonary veins are draining into the superior vena cava or innominate vein, diagnosis through catheterization can be made either by entering the pulmonary vein from the systemic vein or by finding a high oxygen content of the blood samples taken in this vessel in comparison with those of the inferior vena cava. However, when the anomalous pulmonary vein drains into the right atrium, it is impossible to differentiate this condition from an atrial septal defect: both conditions show a step-up in oxygen content in the right atrium in comparison with that taken in the superior and inferior cavae. Even when the pulmonary vein is catheterized, this is not a definite proof that it is draining into the right atrium because it is impossible to tell whether the catheter passed from the right atrium into the anomalous pulmonary vein or through an atrial septal defect and the left atrium into the pulmonary vein.

Dye curves obtained by injecting Evans Blue T-1824 into the right pulmonary artery[9] do not help either because it has been proved that there is a preferential drainage of the right lung into the right atrium in the majority of cases of atrial septal defect. Moreover, anomalous pulmonary veins and atrial septal defect may be associated creating an even greater diagnostic problem.

Atrial septal defect.—Atrial septal defect is one of the most common congenital heart anomalies and an accurate diagnosis becomes of the greatest importance because of its possible surgical closure. Usually the pressure of the left atrium exceeds that of the right by at least one or two mm. Hg.[10] and the blood flows from left to right. Since the left atrial blood is fully saturated with oxygen, there is no cyanosis. The amount of blood shunted across the defect depends upon the size of the artery. This blood flows through the right atrium, right ventricle, pulmonary artery, pulmonary veins and then returns to the right atrium again. This causes some dilatation of the right atrium, right ventricle, and pulmonary arteries. Although an atrial septal defect can be diagnosed clinically with relative accuracy, its definite diagnosis can be established only by catheterization. Cardiac catheterization shows an increased saturation of the blood of the right atrium in comparison with that of the inferior and superior venae cavae. The catheter may be passed through the septal defect. However, this is not a definite proof of a clinically significant defect because passing of the catheter may be accomplished also through a foramen ovale which is patent only from right to left being closed by a valve. This exists in about 25 per cent of normal cases.[11]

Catheterization studies are also of value in the evaluation of the pressure in the right ventricle and pulmonary artery since some patients develop early pulmonary hypertension and such finding may affect the decision regarding surgical closure of the atrial septal defect.[12]

Increase in oxygen content of the right atrium may also be due to:
—rupture of an aortic aneurysm into the right atrium;
—aorta-cava fistula;
—ventricular septal defect plus tricuspid insufficiency;
—A.V. communis with shunt from left ventricle to right atrium; or
—atrial defect (septum primum) with mitral insufficiency.

Ventricular septal defect.—Ventricular septal defect is a less benign malformation than previously thought. Many patients die in early infancy[13] due to heart failure. The defect is usually located in the basal portion of the septum (pars membranacea). Defects of the muscular septum are less common and are considered more benign; it is possible that the defect is reduced in size during ventricular systole,[11] thus causing a smaller shunt. Pulmonary hypertension occurs more frequently when the defect involves the pars membranacea. The difference in pressure between the left and right ventricles causes a shunt from left to right. The amount of blood passing through the defect depends not only upon the size of the defect but also upon the resistance offered by the pulmonary circulation; blood shunted across the defect increases the pulmonic flow and the return to the left heart. Therefore, evidence of enlargement of the left ventricle, right ventricle, pulmonary arteries and left atrium is encountered. The murmur caused by this malformation is usually harsh and loud and is mostly located in the third left interspace. However, a similar type of murmur is also found in atrial septal defects and even in cases with atypical ductus.

Right heart catheterization may furnish definite data in the majority of cases. A step-up in oxygen content of more than 1 volume per cent in the right ventricle is usually found in cases of ventricular septal defect. The association of pulmonary hypertension is more frequent with ventricular than with atrial septal defect. However, it should be noted that an increase of right ventricular oxygen content may also be due to: patent ductus with pulmonic regurgitation; rupture of aortic aneurysm into the right ventricle; or to a streamlined jet of a left-to-right shunt through an atrial septal defect (missed during sampling in the right atrium).

Patent ductus arteriosus.—The diagnosis of patent ductus arteriosus presents no problem when a continuous murmur can be heard over the pulmonic area. The absence of a diastolic component during the first few years of life has been admitted by several authors and has been attributed to small gradient of pressure during diastole between aorta and pulmonary artery.[14] Occasionally, cardiac enlargement and heart failure may occur early in life and a prompt diagnosis may be life saving. Cardiac catheterization may establish a definite diagnosis if the catheter is passed through the ductus into the aorta. On the other hand, failure to catheterize the ductus does not rule out its presence. Arterialization of the blood of the pulmonary artery cannot be considered as a definite proof of patency of the ductus because arterialized blood of the left ventricle may be directly shunted across a ventricle septal defect into the pulmonary artery without admixture of that of the right ventricle. In such cases aortography

is necessary for the differential diagnosis.

Pure pulmonic stenosis.—Pulmonic stenosis without ventricular or atrial septal defect is a relatively common congenital malformation. The stenosis may be valvular, infundibular, or both. The valvular stenosis is caused by a fusion of the cusps which form a diaphragm-like or conical obstruction with a small central orifice of 2 to 4 mm. in diameter, offering great resistance to the flow of blood from the right ventricle to the pulmonary artery. As a result, the right ventricular work increases tremendously and the pulmonary flow is reduced; pressure increases in the right ventricle and decreases in the pulmonary artery, thus creating a "gradient." The pressure of the right atrium is also elevated, even without right ventricular failure. If the foramen ovale is closed, no shunt is possible. Therefore, if there is cyanosis, it is a "peripheral" cyanosis resulting from slow circulation and low cardiac output. Arterial saturation is normal.

A definite diagnosis can be made clinically in the typical cases. However, catheterization is useful, not only for evaluation of the abnormal physiology pre- and post-operatively but also as a way to ascertain the type of stenosis. This differentiation is important since the type of operation depends on the type of obstruction. When there is an infundibular stenosis, a zone of intermediate pressure may be registered while the catheter is withdrawn through the outflow tract of the right ventricle. On the other hand, failure to detect an "intermediate zone of pressure" does not necessarily exclude the existence of infundibular stenosis.

There is a group of patients who clinically show almost no disability, a systolic murmur and split second pulmonic sound, slight evidence of hypertrophy or right bundle branch block, and normal vascularization of the lung fields upon fluoroscopy.[15] The differential diagnosis in this group can be made only by catheterization. Considering that a small "gradient" of pressure between the right ventricle and pulmonary artery has been found in cases of dilatation of pulmonary artery or increased pulmonic flow, there has been discussion about the minimum gradient of pressure necessary for diagnosing pulmonic stenosis. There is general agreement that a minimum of 20 mm. is required in order to establish such a diagnosis.

Since there are cases of pulmonic stenosis with marked elevation of the right ventricular pressure who show slight or no disability, determination of pressure by cardiac catheterization is of great value for the evaluation of the patient for surgery. Even when the patient is symptom-free, if the pressure is higher than 80 mm. of Hg., surgery is advisable, while a pressure higher than 100 mm. Hg. is definite indication for surgery.

The blood samples usually reveal no significant change in oxygen content in the various chambers of the heart. Occasionally, when the opening of the valve is very small and the catheter stays in the pulmonary artery for a long time (care should be taken to avoid this), the oxygen content of the pulmonary artery may become low as a result of the obstruction produced by the catheter and of the diminished cardiac output.

Pulmonary stenosis with patent foramen ovale.—Right atrial pressure is usually high in cases of pure pulmonic stenosis even in the absence of right heart failure. If the foramen ovale is patent, mixed venous blood is shunted from the right to the left atrium. This blood then mixes with the fully saturated blood coming from the lungs and passes to the ventricle and aorta. Therefore cyanosis may be present at birth.

Except for arterial unsaturation of the blood, the data of catheterization are similar to those of pulmonic stenosis with closed septa. The typical cases offer no diagnostic difficulty. Whenever the differential diagnosis with a Tetralogy of Fallot is difficult, catheterization should be done because a Blalock-Taussig operation would be detrimental. A definite diagnosis can be made through cardiac catheterization when the pressure of the right ventricle is much higher than that of the aorta. Then ventricular septal defect and dextroposed aorta can be excluded. When the pressure in the right ventricle and aorta is at about the same level, ventricle-to-face circulation times determined by fluorescein[16, 3] in children, and ether[17] and Evans Blue[18, 19, 20] in adults, also help in ruling out an over-riding aorta.

Tetralogy of Fallot.—This is the most frequent cyanotic malformation of the heart. As well known, it consists of pulmonic stenosis, dextroposition of the aorta, and high ventricular septal defect; right ventricular hypertrophy is a necessary consequence. Infundibular stenosis is the usual finding in Tetralogy of Fallot; however, cases with valvular stenosis are not uncommon.

In typical cases, the aorta overrides the septum by 40 per cent. On account of the pulmonic stenosis, there is an increased resistance for the blood to reach the pulmonary artery and, as a result, blood is shunted from the right ventricle into the aorta causing some unsaturation of the arterial blood. The amount of the shunt will depend on the severity of the stenosis and the degree of overriding.

In the majority of cases the diagnosis can be made clinically.[21] Atypical cases need catheterization; however, sometimes angiocardiography is even more helpful. Catheterization usually shows a normal or low pressure in the pulmonary artery and a high pressure in the right ventricle. The right ventricular pressure should be at about the same level as the aortic pressure. Some degree of left-to-right shunt may be demonstrated by a step up in oxygen content in the right ventricle. Overriding of the aorta is confirmed if the catheter is passed into it. Unfortunately the aorta and pulmonary artery are seldom entered.

A definite diagnosis can be made when low pulmonic pressure and high right ventricular pressure are found; the aorta is catheterized; right ventricular and aortic pressure are at about the same level.

When the aorta is not catheterized, no step-up in the right ventricle is found, and right ventricular pressure is at the same level as the systemic, the ventricle-to-face circulation time is of help for the evaluation of a right-to-left shunt from the right ventricle to the aorta. A short right ventricle-to-face circulation time confirms the diagnosis of Tetralogy of Fallot, while prolonged circulation time would be against it. However,

normal circulation time does not rule out Tetralogy of Fallot.[3, 20] Selective angiocardiography[22] with the catheter in the right ventricle is the ideal method for the evaluation of these cases. It makes possible to visualize the infundibulum, the pulmonary artery and the pulmonary valve, besides showing the overriding aorta. It cannot be a substitute for catheterization because it fails to give information about the hemodynamic changes.

Tricuspid Atresia.—The patient may survive in spite of this condition if there is an atrial septal defect. Blood coming from the cavae and the coronary sinus passes through the atrial defect to the left atrium where it mixes with fully saturated blood coming from the pulmonary veins and then goes to the left ventricle. From this chamber it reaches the systemic circulation through the aorta and also reaches the pulmonary circulation by one of the following routes:

(a) through a ventricular septal defect, a small right ventricle and the pulmonary artery.

(b) through a pulmonary artery arising from the left ventricle;

(c) through patency of the ductus or collateral circulation.

Two basic data are needed in cases of tricuspid atresia:

(1) Pulmonary circulation—The amount of blood reaching the lungs may be reasonably estimated by fluoroscopic and x-ray examination in the majority of the cases, but sometimes it is difficult to determine the need for an anastomosis by clinical means. Catheterization does not help much in getting this information. As is expected the catheter fails to enter the right ventricle. It passes into the left atrium and thence may be passed to the pulmonary veins or left ventricle. The position of the pulmonary artery is such that it is almost impossible to intubate this vessel. The blood that reaches the lungs comes from the left ventricle but it may not be mixed well enough for even an approximated estimation of pulmonary flow. Angiocardiography may be more useful than cardiac catheterization.

(2) Size of the atrial septal defect—When the defect is small, the right atrium has to work against a greater resistance in order to deliver all the blood received from the cavae. As a result, it hypertrophies and dilates. Liver pulsations may be an indication that the septal defect is small and have been observed even in one case proved at autopsy to have a single atrium.[23] The magnitude of the P waves of the ECG may be of value in the evaluation of the right atrial hypertrophy, which in turn would be inversely proportional to the size of the defect. No definite conclusions can be reached at present. Angiocardiography usually gives valuable information about the size of the defect.

Taussig-Bing Syndrome.[24] In this condition, the aorta arises completely from the right ventricle while the pulmonary artery, usually very large, overrides the septum. There also is a ventricular septal defect. Through this defect, some arterial blood from the left ventricle reaches the aorta while

venous blood from the right ventricle reaches the pulmonary artery. Catheterization demonstrates that the blood of the pulmonary artery has a higher oxygen concentration than that of the aorta. The pressures of both vessels are at about the same level. When the defect is small, the patient dies early in life. Attempts to increase the mixture of venous and arterial blood by creating an atrial septal defect have been made in some cases with good results. Catheterization is of help in the evaluation of these cases, prior to surgery, in order to find out if an atrial septal defect already exists, and after surgery in determining the hemodynamic changes due to the operation. In complete transposition of the great vessels, catheterization of the pulmonary artery is more difficult and failure to accomplish this would not permit definite conclusions.

Eisenmenger complex.—This malformation consists of a ventricular septal defect associated with some degree of over-riding of the aorta and right ventricular hypertrophy. Since resistance of the pulmonary vascular bed is less than the systemic, shunting is predominantly left-to-right, at least in an early stage. However, pulmonary vascular changes may develop early in life and, as a result, pulmonary vascular resistance increases and may even become higher than the systemic. Then, a predominant right-to-left shunt occurs. Therefore, the time of appearance of cyanosis is in relationship with the degree of pulmonary resistance. The mild cases of Eisenmenger may be confused with moderate pulmonic stenosis, ventricular septal defect, or even Tetralogy of Fallot. The severe cases may be confused with the Taussig-Bing syndrome.

Cardiac catheterization contributes to the differential diagnosis in the first group of cases by showing:

(a) equal systolic pressure in the right ventricle and pulmonary artery;

(b) low saturation of blood in the femoral artery.

In the second group, catheterization makes possible the demonstration of either a small step-up in oxygen content in the pulmonary artery or none at all. In the Taussig-Bing syndrome, it would show a higher oxygen content in the pulmonary than in the systemic artery, because the pulmonary artery arises from the left ventricle.

Ebstein's Disease.—This anomaly consists of a downward displacement of part of the tricuspid valve and is usually associated with an atrial septal defect. Due to this association, cyanosis is frequently present. Although difficult, a clinical diagnosis may be possible.[25] In some cases, differential diagnosis with a pure pulmonic stenosis can be made only by cardiac catheterization. If the pulmonary artery is entered, the systolic pressure of this vessel is similar to that of the right ventricle. Tricuspid insufficiency, when present, would result in high pressure in the right atrium with little gradient between this cavity and the right ventricle. On withdrawal of the catheter from the ventricle, a change from the ventricular pattern of pressure to an atrial pattern may occur near the apex while no further change takes place at the region of the tricuspid valve[26] (displacement of the tricuspid leaflets).

CONCLUSIONS

Cardiac catheterization is a valuable tool for diagnosis and evaluation of congenital malformations of the heart. Many physical and roentgenological signs have been clarified by this method. However, there is no substitution for a good history and physical examination. The decision to submit a patient to cardiac catheterization should be made only after complete clinical evaluation of the patient. It should be pointed out that certain risks are involved in this procedure. Therefore, only a trained team can undertake this procedure with success.

RESUMEN

La cateterización cardiaca es un procedimiento valioso para determinar y valuar las malformaciones del corazón. Muchos signos físicos y roentgenológicos se han aclarado por este método. Sin embargo, no hay substituto para una buena historia y un buen examen físico. La decisión para someter un enfermo a la cateterización, debe hacerse sólo después de un estudio clínico completo. Debe señalarse que hay ciertos riesgos en el proceder. Por tanto sólo el personal bien preparado puede emprender el método satisfactoriamente.

RESUME

Le cathétérisme cardiaque est une méthode de valeur pour diagnostiquer et évaluer les malformations congénitales du coeur. La signification de nombreux symptômes physiques et radiologiques a été éclaircie par ce procédé. Cependant, il ne peut remplacer un bon interrogatoire, ni un examen physique. La décision de soumettre le malade au cathétérisme cardiaque ne devrait être prise qu'après un complet examen clinique du malade. Il faut signaler que ce procédé comporte certains risques. C'est pourquoi une équipe expérimentée peut seule l'entreprendre d'une façon heureuse.

SCHLUSSFOLGERUNGEN

Die Herzkatheterisierung ist ein wertvolles Hilfsmittel für Diagnostik und Bourteilung der angeborenen Herzfehler. Viele physikalische und röntgenologische Merkmale wurden durch diese Methode aufgeklärt. Jedoch gibt es keinen Ersatz für eine gute Anamnese und klinische Untersuchung. Die Entscheidung, einen Patienten der Herzkatheterisierung zu unterziehen, sollte erst dann gafällt werden, wenn eine vollkommen abgeschlossene klinische Untersuchung des Patienten vorliegt. Es wird darauf hingewiesen, dass mit der Katheterisierung, ein gewisses Risiko verbunden ist. Deswegen kann nur eine geübte Gruppe diesen Eingriff mit Erfolg durchführen.

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Cardiac Catheterization in Acquired Lesions of the Heart or Lungs*

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Right heart catheterization is not only useful as one of the diagnostic procedures in congenital heart diseases but is also useful for studying the changes of pulmonary circulation in mitral stenosis and chronic pulmonary diseases.

Primary pulmonary hypertension, which is indeed a rare condition, has a special place. Diagnosis of this condition during life is tentative and is based on data obtained through cardiac catheterization. However, a definite diagnosis can be made only after autopsy, by excluding any possible cause of secondary pulmonary hypertension. Dresdale and coworkers[1] reported four cases, three of whom had cardiac catheterization.

The characteristic clinical features[2, 4] of *primary pulmonary hypertension* are: syncope on effort, slight exertional dyspnea but no orthopnea, peripheral edema, cyanosis, electrocardiographic and roentgenologic evidence of right ventricular hypertrophy, accentuated second pulmonary sound (sometimes followed by a diastolic murmur) and prominent pulmonary artery with no evidence of left atrial enlargement in the roentgenogram.

Right heart catheterization supplies several important data including pulmonary arterial and pulmonary wedge pressures, and cardiac index at rest and during exercise. This procedure is essential in order to rule out the possibility of a left-to-right shunt[5, 9] and the secondary pulmonary hypertension due to conditions other than increased flow (see Table I).

The presence of a *left-to-right shunt* in atrial septal defect, ventricular septal defect, and uncomplicated patent ductus arteriosus can be easily differentiated from the primary pulmonary hypertension by means of cardiac catheterization. The recognition of a *two-way shunt* in cases of arterial septal defect also offers no difficulty. A complete *right-to-left shunt* is seldom encountered in pure atrial septal defect with the exception of cases in congestive heart failure in whom right atrial pressure exceeded the left. Primary pulmonary hypertension with closed foramen ovale has a normal arterial saturation. Cases with an Eisenmenger complex exhibit identical blood pressure in the pulmonary and systemic arteries while the arterial blood has an incomplete oxygen saturation, especially during exercise. When reversed shunt occurs in patent ductus arteriosus, there may be a normal arterial oxygen saturation in the right brachial artery while there is a lower arterial saturation in the left brachial and in the

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femoral arteries. Pulmonary wedge pressure is elevated in mitral stenosis or left heart failure while it is normal in primary pulmonary hypertension. One of our cases of mitral stenosis had normal pulmonary arterial pressure and elevated wedge pressure while at rest, but the former became elevated during and immediately after three minutes of mild exercise.

Right heart catheterization may give similar data in *chronic cor pulmonale* with elevated pulmonary arterial pressure and in primary pulmonary hypertension. But the clinical, roentgenological and laboratory findings (including pulmonary function studies) easily permit to differentiate the two conditions.

Studies of pulmonary circulation in *acute cor pulmonale* caused by *large pulmonary emboli* are not possible on account of the rapid course and the critical conditions of the patients. How rapid is the course of these patients has been shown by Neuhof and Klein.[10] Sixty-nine out of 88 fatal cases died within 24 hours. On the other hand, *chronic pulmonary diseases* have a slower course and are important because *chronic*

TABLE I

	Right ventr. pressure	Pulmonary A. pressure	PCP	Lt.-to-rt. shunt	Rt.-to-lt. shunt	Art. O_2 sat.
Primary pulmonary hypertension	Increased (same as PA press.)	Increased (may be higher than syst. press.)	Normal	None	None	Normal
Ventr. septal defect	Norm. or slight inc.	Norm. or slight inc.	Normal	Usually present	Seldom occur	Normal
Atrial septal defect or anomolous pulm. venous return	Normal or increased	Normal or increased	Normal	Usually present	May be present	Normal
Eisenmenger complex	Elevated systolic = systemic S.	Elevated systolic = systemic S.	Normal	Seldom	Present	Decreased
Patent ductus arteriosus	Normal or elevated	Normal or elevated	Normal	Usually	Usually none but may be present	Normal (except in case with pulmonary hypertension)
Mitral stenosis	Usually elevated in severe late cases	Usually elevated in severe cases	Elevated	None	None	Normal
Left heart failure	May be elevated	May be elevated	Elevated	None	None	Normal
Constrictive pericarditis over left ventricle	Usually elevated	Usually elevated	Elevated	None	None	Normal
Chronic cor pulmonale	Elevated (from slight to severe)	Elevated (from slight to severe)	May be Normal	None	None	Normal or decreased

cor pulmonale accounts for about six per cent of all cardiac conditions at autopsy.[11] Diagnosis of chronic cor pulmonale is seldom made before the appearance of symptoms and signs of cardiac failure and is also frequently not made during life, so that in 40 per cent of the patients who died of chronic cor pumonale, correct diagnosis was made only at autopsy. The prognosis is severe because from 60 to 86 per cent of patients described in the literature died at the first episode of cardiac failure.[11, 12]

Pulmonary wedge pressure is obtained by wedging the tip of the catheter in a branch of the pulmonary artery. With this technique, Hellem, Haynes, and Dexter[13] demonstrated that pulmonary capillary pressure is normal in emphysema and other chronic pulmonary diseases while it is elevated in mitral stenosis and in conditions causing left heart failure. Thus, determination of pulmonary wedge pressure is of importance in the differential diagnosis of these conditions.

Various authors[14, 15] observed that mean right atrial pressure and the diastolic pressure of the right ventricle were normal in cases of chronic pulmonary disease without congestive failure. Also, in the absence of clinical evidence of heart failure, one-third of the patients with obstructive emphysema had elevated pulmonary systolic pressure varying from 39 to 49 mm. Hg. It is known that, in the absence of pulmonic stenosis, the systolic pressures of the right ventricle and the pulmonary artery are identical. When the right heart fails, in addition to elevated systolic pulmonary pressure, the diastolic pressure of the right ventricle increases, and soon mean right atrial pressure also becomes elevated.[14, 16]

Table II includes selective data from catheterization obtained by various investigators in chronic pulmonary diseases with emphysema. According to early authors, the arterial oxygen saturation was either normal or low, and the cardiac index was higher than that of normal subjects at rest. However, the cardiac index of patients with normal arterial saturation was similar to that of those with low arterial saturation. The average arterial oxygen saturation in 10 cases[17] of cor pulmonale with emphysema was 75.1 per cent and the average cardiac index was 2.7.

The frequently found high cardiac output in patients with pulmonary emphysema with or without cor pulmonale needs explanation. The higher pulmonary arterial pressure with lower arterial saturation would indicate a severely advanced stage of pulmonary emphysema. It is known that, while expiration in normal subjects is effortless and passive, considerable exertion is necessary for an emphysematous patient to exhale. Therefore, it would not be surprising to realize that emphysematous patients in the so-called basal state during cardiac catheterization need more effort for their respiration. This may account for part of the high cardiac output in the early stage of pulmonary emphysema.

Although the pulmonary arterial tree is so distensible that unilateral resection of the lung causes no significant increase in pulmonary pressure, pulmonary arterial pressure rises in late stages of pulmonary emphysema, even at rest, on account of significant changes of the pulmonary arterial bed. There is an increased resistance of the pulmonary arterial bed

TABLE II

		Arterial O_2 per cent sat.	Cardiac index L/min./M^2	Pul. artery systolic	Pul. artery diastolic	Mean P.A. pressure
Hickam and Cargill, J. Clin. Invest. (1948)	Emphysema 5 cases average figure	89 90	3.9 5.0			24 at rest 35 exercise
Riley, Motley, Cournand et al. Am. J. Physiol. (1948)	Emphysema pul. fibrosis	96 93	4.4 5.7	16 23	4 11	9 at rest 15 exercise
	Emphysema and pul. fibrosis	93 86	3.48 —	24 59	4 27	13 at rest 43 exercise
Our cases	Emphysema	82	—	52 78	26 40	39 at rest 59 exercise
	Cor pulmonale* mild right heart failure	100	—	40	22	28 at rest only
Fowler, Westcott, Scott and Hess Circulation (1952)	10 cases of cor pulmonale with emphysema	75.1	2.7	64	30	—

* Mean right atrial pressure was 13.2 mm. Hg.
right ventricular pressure was 36/6 mm. Hg.

which probably tends to prevent an increase in cardiac output if it occurs in the early stages of pulmonary emphysema.

Interesting data on *emphysema* can be found in a study of Riley et al.[18] The first patient had normal arterial oxygen saturation and normal pulmonary arterial pressure both at rest and during exercise. The second case, a 40 year old man, exhibited poor arterial saturation and elevated PA pressure (59/27 mm. Hg.) only during exercise. On the contrary, one of our patients showed poor arterial saturation (82 per cent), normal cardiac output, and elevated P.A. pressure at rest. During exercise, the P.A. pressure rose further (from 52/26 to 78/40) but returned to 52/23 mm. Hg. three min. after exercise. Another of our cases exhibited evidence of mild right heart failure as proved by catheterization because the diastolic pressure of the right ventricle and the mean right atrial pressure were significantly elevated. It seems likely that the above four examples may represent various stages in the development of cor pulmonale due to chronic obstructive emphysema.

Following determination of mean pulmonary arterial pressure and cardiac output by means of the direct Fick principle, it is possible to calculate the pulmonary resistance of both lungs and the amount of work performed by the right ventricle. This can be done by using the following conventional formulae:

$$\text{Pulmonary resistance} = \frac{\text{P.A. mean} \times 1.332}{\text{Cardiac output}} \times 60 = \text{dynes sec. cm.}^5$$

$$\text{Work done of R.V.} = \text{C.O.} \times \text{P.A. mean systolic} \times 1.332 = \text{joules}$$

The use of the systolic pressure instead of the mean P.A. pressure has been advocated for the work done by the right ventricle,[18] 10-40 per cent higher data for this work were obtained. We feel that the use of

mean systolic pressure is more reasonable than that of mean pulmonary arterial pressure in conventional formulae.

The findings of catheterization confirm the clinical impression, e.g. that only a small percentage of the patients with chronic obstructive emphysema develop "cor pulmonale," even after many years. The data supplied by right heart catheterization in chronic emphysema vary greatly from patient to patient. The following suggestions concerning the mechanism of chronic cor pulmonale may give some explanation.

(1) *Degree of pulmonary emphysema.* The residual air volume varies from 30 to 60 per cent of the total lung volume in chronic obstructive emphysematous patients. It has been assumed for a long time that emphysema causes pulmonary hypertension and ultimately cor pulmonale by progressive obliteration of the capillaries within the lungs. However, a lack of correlation between severity of emphysema and cardiovascular changes has been shown.[20, 21] One study[21] was only based on x-ray determination of the cardiac size on posteroanterior radiogram plus the evaluation of the residual air and the total lung volume ratio of patients. The degree of pulmonary hypertension was only estimated and not determined. It should be concluded that the problem of the relationship between the degree of emphysema as determined by residual air and total lung volume ratio, on one hand, and pulmonary hypertension and right ventricular hypertrophy on the other, is still not solved. It is likely that other factors are present, in addition to the mechanical distention of the lungs leading to changes of the pulmonary arteries. A thorough microscopic study of the changes of the pulmonary vascular bed and its estimated size in addition to the study of changes of the bronchial tree would present great interest in emphysematous patients with or without right ventricular hypertrophy or pulmonary hypertension.

(2) *Amount of daily physical work.* It has been known that normal persons may develop transient emphysema after strenuous exercise. Although normal subjects usually present no change of pulmonary arterial pressure during exercise, a slight elevation (2 to 3 mm. Hg.) has been observed by us, as well as by others. Exercise increases the work done by the right ventricle when this receives an increased venous return, especially if it is working against the higher resistance imposed by a poorly distensible pulmonary vascular bed.

CONCLUSION AND SUMMARY

Right heart catheterization is the only practical mean to verify the clinical diagnosis of primary pulmonary hypertension during life. The differential diagnosis of this syndrome is briefly discussed. Studies of right heart catheterization in patients with chronic obstructive emphysema have demonstrated the following data:

1. Cardiac output is increased at rest in a certain number of cases, but this finding is not the rule, especially in late stages.

2. Pulmonary resistance may be increased at rest and shows a further increase during exercise.

3. Right ventricular work is markedly increased during physical exercise.

4. Different findings of pulmonary arterial pressure, arterial O_2 saturation, and cardiac output in different patients may reflect a different extent or type of vascular changes, possibly because the patients were in different stages of an evolutionary process.

CONCLUSIONES Y RESUMEN

El único medio práctico para diagnosticar la hipertensión primitiva pulmonar, es el cateterismo del corazón derecho.

Se discute brevemente el diagnóstico diferencial de este síndrome. Los estudios de tales cateterizaciones han demonstrado lo siguiente:

1. El rendimiento cardiado está aumentado en reposo en ciertos casos, pero esto no es la regla, especialmente en etapas tardías.

2. La resistencia pulmonar puede aumentarse en reposo y muestra ulterior aumento durante el ejercicio.

3. El trabajo del ventrículo derecho aumenta marcadamente durante el ejercicio.

4. Diferentes hallazgos de la presión de la arteria pulmonar, saturación de 02 arterial, y rendimiento cardiaco en diferentes enfermos puede ser por la diferencia en extensión de los cambios vasculares posiblemente porque los enfermos se encontraron en diversas etapas evolutivas.

RESUME

Le cathétérisme du coeur droit est le seul moyen pratique de vérifier le diagnostic clinique d'hypertension pulmonaire primitive durant la vie. L'auteur discute brièvement le diagnostic différentiel de ce syndrome. Des études sur le cathétérisme du coeur droit chez les malades atteints d'emphysème chronique obstructif ont montré les faits suivants:

1. Le débit cardiaque est augmenté au repos dans un certain nombre de cas, mais cette constatation n'est pas de règle, particulièrement dans une phase tardive de l'évolution.

2. La résistance pulmonaire peut être accrue au repos et montrer une augmentation soutenue pendant l'exercice.

3. Le travail du ventricule droit est augmenté d'une façon nette pendant l'exercice physique.

4. Différentes constatations concernant la pression artérielle pulmonaire, la saturation artérielle oxygénée et le débit cardiaque chez différents malades peuvent refléter des modifications vasculaires d'étendue et de type différent, peut-être parce que les malades ont été vus à différentes phases du processus évolutif.

SCHLUSSFOLGERUNG UND ZUSAMMENFASSUNG

Die Katheterisierung des rechten Herzens ist der einzige praktische Weg, die klinische Diagnose einer primären Lungenhypertension am lebenden Kranken zu bestätigen. Die Differentialdiagnose des Syndroms wird kurz erörtert. Untersuchungen von Kranken mit chronischem obstruktivem Emphysem mittels Katheterisierung des rechten Herzens führten zu folgenden Ergebnissen:

1. Das Schlagvolumen des Herzens in der Ruhe ist in einer gewissen Anzahl der Fälle erhöht; dieser Befund ist aber, besonders in den späten Stadien, nicht die Regel.

2. Der Widerstand in der Lunge bei Ruhe kann erhöht sein und zeigt einen weiteren Anstieg während körperlicher Übungen.

3. Die Arbeitsleistung der rechten Herzkammer ist während körperlicher Übung erheblich erhöht.

4. Verschiedenartige Befunde des Druckes in den Lungenarterien, der arteriellen Sauerstoffsättigung und des Schlagvolumens des Herzens bei verschiedenen Kranken können eine Verschiedenheit der Ausdehnung oder der Art der Gefässveränderungen wiederspiegeln, möglicherweise weil die Kranken sich in unterschiedlichen Stadien eines sich entwickelnden Prozesses befanden.

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Physiological Effects of Exsufflation with Negative Pressure (E.W.N.P.)

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The method of producing rapid expiratory flow rates of air from the lungs has been termed Exsufflation With Negative Pressure,[1, 2, 3] or E.W.N.P. Since the apparatus, shown in Figure 1,* is capable of producing intrathoracic pressure changes greater than those effected by pressure breathing devices currently available, studies were made on the effects of E.W.N.P. on the cardiovascular system and, because of its use in post-operative patients with surgical wounds of the abdomen,[4] on the changes in intra-abdominal pressure during this procedure. The changes in position of the diaphragm during E.W.N.P. in patients with an ineffective cough were also found of interest as an indication of the degree of aeration and deflation of the lungs accomplished by this apparatus.

The purpose of this report is to summarize the results obtained from determining the effect of E.W.N.P. on the following functions: heart rate electrocardiogram, arterial blood pressure, venous pressure, cardiac output, intragastric pressure, and motion of the diaphragm in normal subjects and in patients whose spontaneous cough is ineffective.

Principle of Operation

Exsufflation With Negative Pressure is a method of mechanical coughing which utilizes (1) a gradual build-up of positive pressure of 20 to 40 mm. Hg. over a period of 1.5 to 2.5 seconds to achieve a full inflation of the lungs and a dilation of the bronchial tree[1, 5] and (2) a swift fall in pressure to 40 mm. Hg. below atmosphere. This pressure drop of 60 to 80 mm. Hg. beginning at the peak of the inspiratory phase results in a sudden expansion of the intrathoracic gases of 1/12th to 1/9th of the total lung volume. The kinetic energy of the current of air due to the establishment of a pressure gradient between the alveoli and the mouth is responsible for the movement of mucus from the smaller bronchi to the upper respiratory tract. During the expiratory negative pressure phase, volume flow rate of air are achieved which are often as high as those produced by a normal subject during his maximal natural cough.[1] This mouthward directed high expiratory velocity includes the explosive decompression effect in expelling sputum, foreign bodies, or a thorotrast mixture toward the mouth.[5] The expiratory phase is completed with the application of 40 mm. Hg. negative pressure for 1 to 1.5 seconds at the mouth. During this phase emptying of the lungs occurs. The apparatus

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*This apparatus is manufactured by the Oxygen Equipment Manufacturing Company, East Norwalk, Conn.

is applied to the patient by means of a mask or mouthpiece. The sequence of pressure changes occurring at the mouth (the intramask pressure) is shown in Figure 2.

The unconscious patient is treated with the neck in a hyperextended position and frequent pharyngeal suction accompanies the procedure. The conscious patient is requested to allow the chest to be passively inflated without voluntary effort. Exsufflation With Negative Pressure has been used successfully in the relief of dyspnea and partial bronchial obstruction by elimination of mucous and purulent plugs or blood clots, as well as aeration of atelectatic lungs, in patients with poliomyelitis, Guillain-Barre syndrome, myasthenia gravis, paraplegia due to cerebral injury, fractured ribs, pulmonary emphysema, bronchial asthma, bronchiectasis and in various postoperative pulmonary complications.[2, 3]

FIGURE 1: The portable E.W.N.P. apparatus is designed with adjustments for volumes, pressures and respiratory cycle timing. Separate outlets for inspiratory and expiratory airflows, containing a filter on the inspiratory side, are new additions to the original design for the prevention of cross-contamination of the two sides.

Methods

Electrocardiographic changes due to E.W.N.P. were observed during a control period of the patient's normal respiration and the period of E.W.N.P. The heart rate was computed from the electrocardiographic record. The electrical axis was determined from the AVR, AVL, AVF and V4 leads.[6] X-ray films of the chest were taken during the maximal voluntary inspiratory and expiratory positions and compared with those produced by the mechanically-induced inspiration and expiration pressures of plus 40 mm. Hg. and minus 40 mm. Hg. Intramask pressures were determined by means of Statham pressure transducer through a Sanborn amplifier on a Sanborn Viso-cardiette. Venous pressure recordings were performed simultaneously on the same equipment. The blood pressure was taken indirectly by means of a sphygmomanometer during a control period and in the course of E.W.N.P. A pressure transducer amplifying and recording system was used in the determination of the intragastric pressures using thin rubber balloons, inflated moderately and located in the stomach.[7] Normal subjects, pre- and postoperative patients, and those with bronchopulmonary diseases were tested. The subjects were thoroughly trained in the use of E.W.N.P. prior to each experiment. The cardiac output was determined in a normal subject by the radioactive sodium dilution technique[8, 9] during a control period and E.W.N.P. The value of this method in recording consistent absolute values has not yet been established. In most instances five exsufflations with E.W.N.P. were given in succession eight to 10 times in a row. For the purpose of presentation in this report the data were averaged and summarized. The pressure

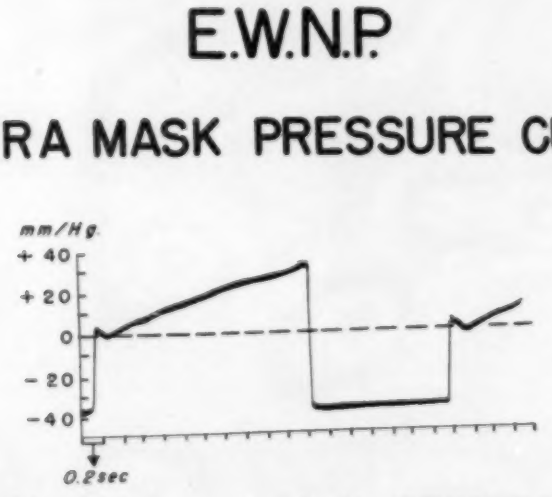

FIGURE 2: Intramask pressure curve produced by (E.W.N.P.). Following a gradual rise of positive pressure in inspiration to 40 mm. Hg. above atmosphere in two seconds, a sudden pressure drop to 40 mm. Hg. below atmosphere occurs in 0.04 seconds. The negative pressure is maintained for approximately 1.5 seconds.

recording equipment was standardized immediately before and immediately after the recordings of intramask, intragastric, and venous pressures. The changes in gastric pressure were compared during normal ventilation, hyperventilation, natural cough, and E.W.N.P. The changes in venous pressure during normal ventilation, natural cough, and E.W.N.P. were similarly compared.

Results

Effect of E.W.N.P. on Heart Rate, Blood Pressure, and Electrical Axis of the Heart. Six normal subjects and six with pulmonary emphysema revealed an average increase in heart rate of 17 to 10 beats per minute respectively during the application of E.W.N.P. as compared to the control period. Two subjects revealed no change. Of 22 patients and normal subjects in whom blood pressures were taken, a slight but insignificant rise in blood pressure occurred during E.W.N.P. The range of blood pressure during the control period was from 190 to 105 mm. Hg. systolic and from 110 to 68 mm. Hg. diastolic. The mean increase in systolic pressure was 8 mm. Hg., and in the diastolic pressure 4 mm. Hg. On inspiration with E.W.N.P. the electrical axis of the heart in six normal subjects and six patients with emphysema was changed in a manner similar to that indured by a full normal inspiration. Similarly, no difference in electrical axis was observed when the electrocardiogram during normal expiration

TABLE I
INCREASE IN PEAK VENOUS PRESSURE OVER CONTROL PERIOD

	(mm H_2O)	
Experiment Number	During E.W.N.P.	During Natural Cough
1	10	180
2	10	
3	0	110
4	0	110
5	0	
6	20	230
7	60	180
8	40	230
9	40	
10	110	
11	150	180
12	50	230
13	70	70
14	10	80
15	130	260
16	130	80
17	140	
AVERAGE	58	161

was compared to the expiratory phase of E.W.N.P. during the application of 40 mm. Hg. pressure below the atmosphere.

Effect of E.W.N.P. on Venous Pressure. In 12 normal subjects, patients with bronchopulmonary disease and poliomyelitis, the venous pressure rise during their own natural cough above the control level averaged 161 mm. of water. During E.W.N.P. the average rise in peak venous pressure in 17 subjects with bronchopulmonary disease and poliomyelitis was 58

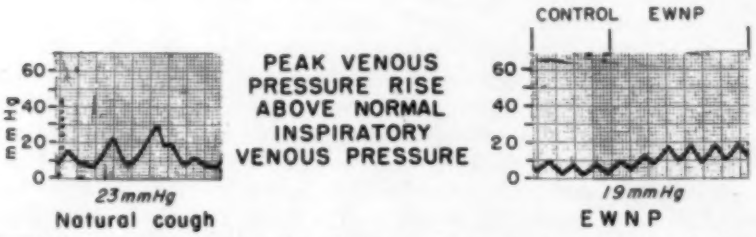

FIGURE 3: Tracings, representing the venous pressure rises occurring during the voluntary cough and E.W.N.P. in a normal subject.

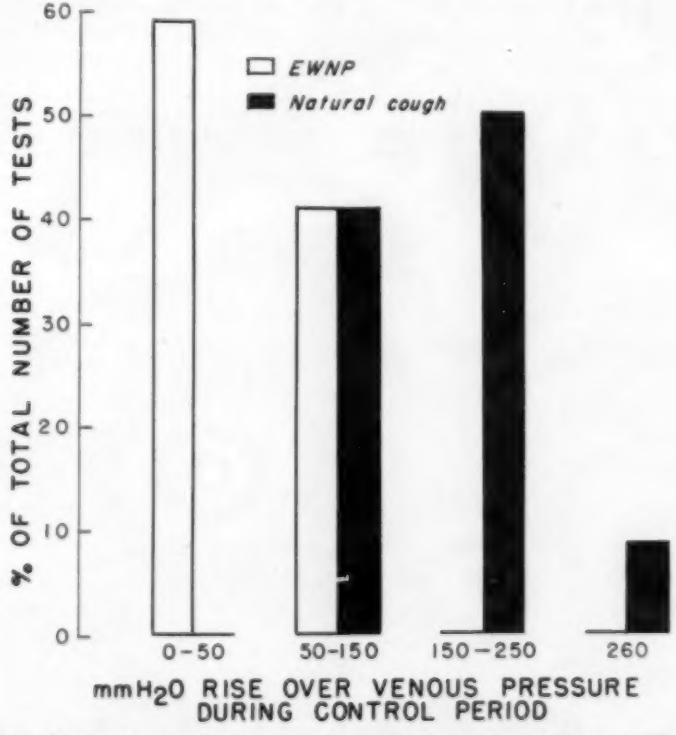

FIGURE 4: In 17 patients with bronchopulmonary disease the venous pressure rise over the resting (control) venous pressure with E.W.N.P. did not exceed 150 mm. H_2O. During the natural cough in 12 patients the venous pressure rise ranged from 50 mm. H_2O to 260 mm. H_2O.

mm. H_2O. (Table I). The difference of the venous pressure changes during E.W.N.P. and a maximal natural cough are shown in Figure 3. The venous pressure changes occurring during natural coughing and E.W.N.P. in subjects with bronchopulmonary disease are shown in Figure 4.

Effect of E.W.N.P. on Cardiac Output. The radioactive sodium method of determining cardiac output was used in one subject. The total cardiac output in litres per minute was 4.5, 4.6 and 4.8 during the control period, and 6.8 liters per minute during E.W.N.P. at plus 30 and minus 40 mm. Hg. pressure, an increase of 2.1 litres per minute.

Effect of E.W.N.P. on Position of the Diaphragm. The position of the diaphragm in nine subjects with pulmonary emphysema was compared during both voluntary inspiration and inspiration produced by a positive pressure of 30 mm. Hg. and during voluntary expiration and expiration produced by a negative pressure of 40 mm. Hg. Increases in descent of the diaphragm induced by E.W.N.P. were 1 to 3 cm. above that recorded in voluntary inspiration in five of the nine patients. An increase in the ascent of the diaphragm during E.W.N.P., compared to normal expiration, occurred

TABLE II
THE EFFECT OF POSITIVE AND NEGATIVE PRESSURE ON THE POSITION OF THE DIAPHRAGM

	Increase in descent +30 mm. Hg. inspiration over normal inspiration	Increase in ascent —40 mm. Hg. expiration over normal expiration
No change	2	5
Less than 1 cm.	2	2
1 cm. to 2 cm.	2	2
2 cm. to 3 cm.	3	0

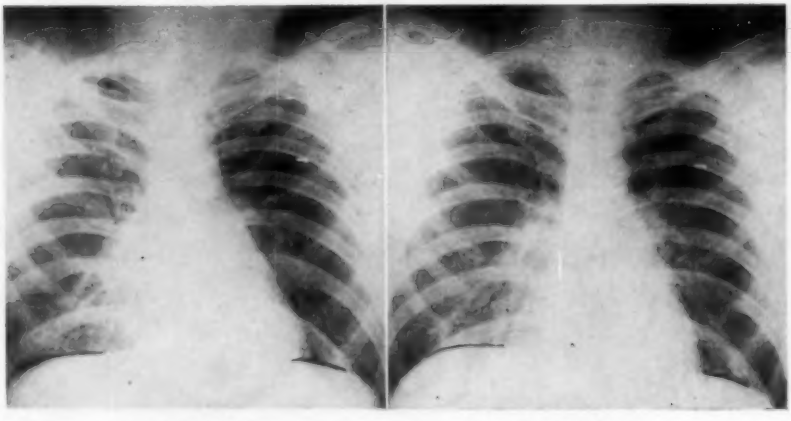

FIGURE 5A FIGURE 5B

Figure 5: Chest x-ray during natural inspiration (*A*) and expiration (*B*) in a patient with pulmonary fibrosis and emphysema reveals markedly diminished diaphragmatic excursion.

in four of the nine patients (Table II). These changes are illustrated in Figures 5 and 6.

Effect of E.W.N.P. on Intragastric Pressures. In nine patients the peak and mean intragastric pressure changes during normal breathing and hyperventilation were determined. The average peak and mean pressure changes during hyperventilation were 15.5 and 7.3 mm. Hg. as compared to 7.11 and 3.7 mm. Hg. during normal breathing respectively. In 10 patients the intragastric pressures with E.W.N.P. were 26 mm. Hg. as compared to 7.1 mm. Hg. during normal ventilation. During a natural cough the average peak pressure of 10 subjects was over 85 mm. Hg. and the average mean pressure 32.4 mm. Hg. The individual cases are sum-

TABLE III
PEAK INTRAGASTRIC PRESSURE CHANGES DURING NATURAL AND MECHANICALLY INDUCED RESPIRATION

	Peak Intragastric Pressures—mm. Hg.			
Subject	Normal Ventilation	Hyperventilation	E.W.N.P.	Natural Cough
1	2.5	3.6	21.0	90+
2	4.0	10.0	7.0	90+
3	2.4	22.0	58.0	90+
4	12.0	14.0	27.0	78
5	12.0	20.0	58.0	90+
6	4.0	26.0	42.0	62
7	3.1	4.2	4.0	90+
8	25	26.0	21.0	82
9	4.0	14.0	11.0	90+
10	2.1	....	11.0	90+

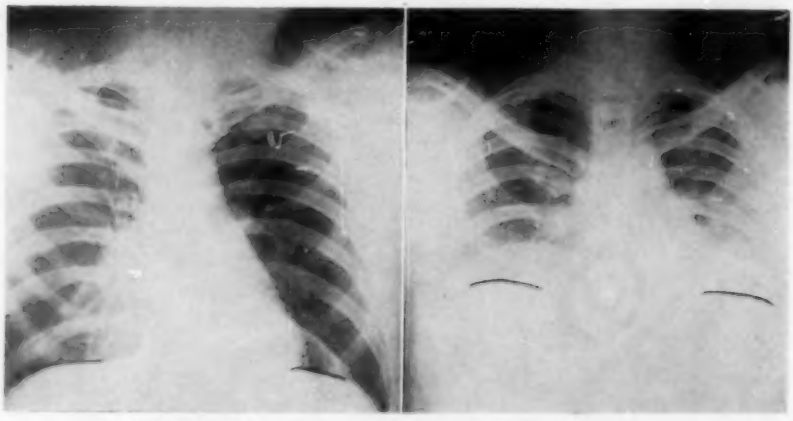

FIGURE 6A FIGURE 6B

Figure 6: Chest x-ray of the same patient revealed much greater diaphragmatic motion between inspiration (*A*) and expiration (*B*) induced by E.W.N.P. as compared to voluntary respiration, seen in Fig. 5.

marized in Table III and in Figure 7. The intragastric pressure curves obtained in a normal subject during hyperventilation, E.W.N.P., and coughing are shown in Figure 8. Similar intragastric pressure curves in a patient with pulmonary emphysema are shown in Figure 9.

Discussion

Exsufflation With Negative Pressure, a method developed for the mechanical elimination of retained secretions, functions by means of a specially-designed alternating positive-negative pressure-type respirator. The intramask pressures are produced by the pressure and vacuum side of a blower unit: the gradual introduction of a volume of air sufficient to produce nearly maximal inflation of the lungs, utilizing a pressure head of 20 to 40 mm. Hg. above atmosphere over a period of 1.5 to 2.5 seconds, produces cardiovascular effects similar to those described in tank exsufflation, an earlier method of mechanical coughing.[10] Since the pressure curve drops swiftly from 40 mm. Hg. above atmosphere to atmosphere in exsufflation, the mean effective positive pressure applied within the chest during the respiratory cycle is relatively low. In E.W.N.P. a still lower mean pressure is produced because of the high negative pressure during expiration. Pressure breathing has previously been shown to effect rises in venous pressure which were more marked in cases with congested and less compliant lungs than those of normal subjects.[11]

The compensatory venous pressure rise was found to be dependent on the applied mean intrapulmonary pressure whether intermittent or continuous positive pressure was used and amounted to about 40 per cent of the applied intramask pressure.[12, 13, 14, 15, 16] In normal subjects in whom

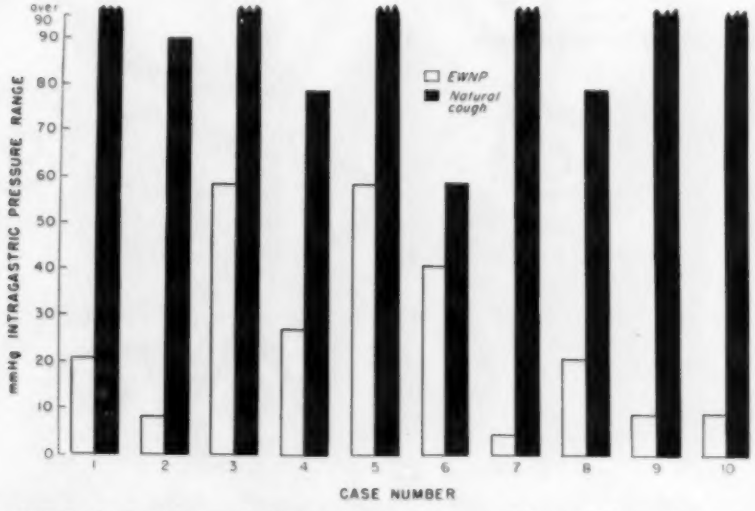

FIGURE 7: A graph of peak intragastric pressures reveals a much greater pressure rise during the naturally induced cough than during E.W.N.P. in 10 normal subjects and patients with bronchopulmonary disease.

the applied mean pressure is between plus 10 to 15 mm. Hg., a lowering of the cardiac output and a lengthening of the circulation time generally was found to occur. The increased amount of blood returning from the peripheral venous circulation during intermittent expiratory negative pressure breathing resulted in a lowering of venous pressure.[17] The combination of inspiratory positive and expiratory negative pressure was more beneficial as an artificial respiration technique in experiments on dogs whose circulation was seriously impaired than intermittent positive pressure breathing.[18] This has been recently confirmed clinically.[19, 20]

Exsufflation With Negative Pressure in subjects with relatively stable circulatory systems produced only minimal changes in arterial blood pressure and a slight rise in heart rate. The rise in venous pressure, averaging 5.8 cm. of water throughout the entire cycle of E.W.N.P., is higher than what would be expected with the mean intramask pressures obtained on this series of normal subjects. Since the inspiratory volume increases with the duration of inspiration,[21] variations in venous pressure response due to E.W.N.P. depend in part on the lung volume of the subject. Also, larger venous pressure rises occurred in patients whose full cooperation was not enlisted during the experimental procedure, i.e., those in whom contracture of the thoracic musculature resulted in undue resistance to the inspiratory air flow. A greater venous pressure rise takes place under these circumstances than when passive inflation of the chest occurs

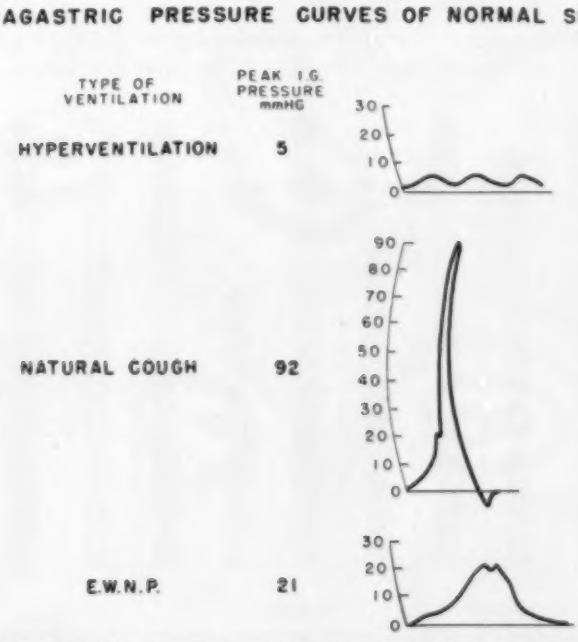

FIGURE 8: Intragastric pressure curves in a normal subject show a markedly higher peak during a spontaneous cough than during E.W.N.P. and hyperventilation.

during the positive pressure phase. An increased venous pressure has been previously noted after the application of a compressing bandage or vest around the chest, which increases the rigidity of the thorax and thus transmits the increased intrapulmonary pressure to the peripheral venous reservoir.[13] The increase in venous pressure during external chest compression may finally become as large as the applied mean positive pressure which was noted in subjects with "elastic" lungs; in the latter cases passive expansion of normal lung tissue absorbs 60 per cent of the pressure.

The moderate increase in cardiac output produced by E.W.N.P. in the one patient reported may possibly be ascribed to a combination of two factors: first, the negative pressure phase of the intramask pressure in this particular experiment was larger (minus 40 mm. Hg.) than the positive pressure phase (plus 30 mm. Hg.) resulting in a subatmospheric mean mask pressure throughout the respiratory cycle and conceivably a larger venous return to the heart over the period of the 10 cycles of E.W.N.P.

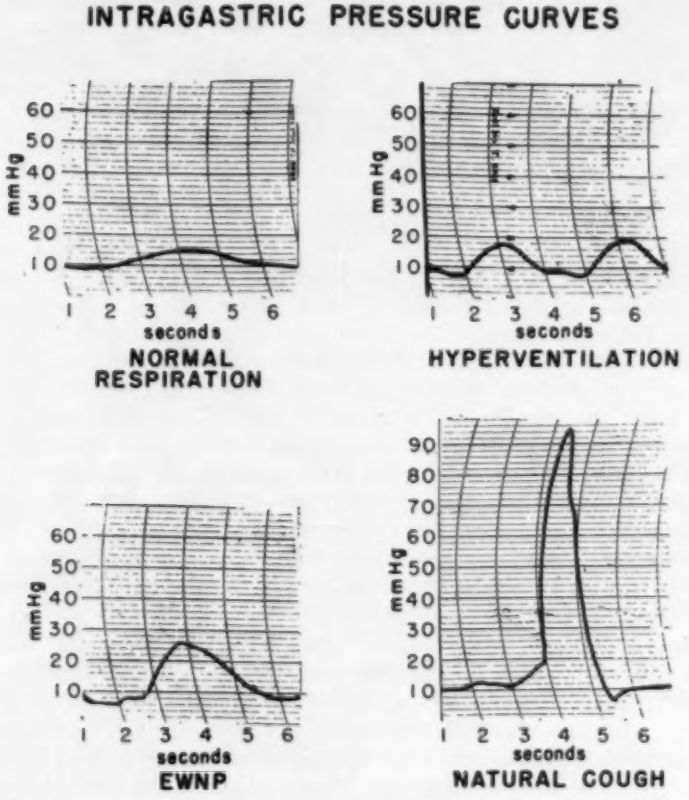

FIGURE 9: In a patient with pulmonary emphysema the peak intragastric pressure rise during spontaneous coughing is much greater than during E.W.N.P., hyperventilation and quiet respiration. The magnitude of peak pressures is similar to that of the normal subject.

than during the control period. Second, hyperventilation produced by the use of E.W.N.P. may have increased the cardiac output. The first explanation, assuming an increased venous return, appears less likely because of the consistent increase in venous pressure occurring during E.W.N.P.

It was apparent that the hyperventilation produced by E.W.N.P. in patients with bronchopulmonary disease caused diaphragmatic motion greater than that produced by the patient's own inspiratory or expiratory effort in some cases. A similar situation had been previously noted in patients in whom diaphragmatic motion was impaired by paralysis due to poliomyelitis.[3] In patients with pulmonary emphysema increased diaphragmatic motion whether produced by E.W.N.P., the head-down position, or training in diaphragmatic breathing,[23] is an important contributory factor in improving ventilation of the alveoli of the lower lobes and drainage of their respective bronchioles.

A comparison between the mean venous pressure increases during E.W.N.P. and natural coughing reveals a much more pronounced rise during the human cough. The changes found indicate that the intrathoracic pressure rise produced by muscular contraction occurring during a natural cough are much higher than those of the positive pressure phase of E.W.N.P. The efficiency of the natural cough, however, is not entirely dependent on the pre-expulsion build-up of intrathoracic pressure. The high intrathoracic pressure head, is designed to facilitate the production of high expiratory velocities in an attempt to propel sputum through the larynx. In patients with pulmonary emphysema, the production of high intrathoracic pressures during the glottis-closure phase of the natural cough and the subsequent pressure drop may result in an even greater pressure difference between the alveoli and lumen of the bronchioles than that normally present.[24] This high alveolar-bronchial gradient may result in a premature closure of the bronchioles and complete obstruction to flow of air from the alveoli to the larger bronchi. The high intrathoracic pressures produced by these patients during coughing are thus frequently ineffective in moving sputum from the bronchioles to the upper respiratory tract. Since high expiratory volume flow rates may be achieved with presumably low intrathoracic pressures during E.W.N.P., it may be an effective means for the elimination of sputum in emphysematous patients, i.e., in delivering it to the area of tracheal bifurcation where it may be expectorated.

Patients with abdominal wounds often have great difficulty with the elimination of sputum during the postoperative period. Elevation of the diaphragm due to gaseous distention with diminished diaphragmatic motility, pain during coughing due to the necessity for contraction of the abdominal musculature during the period of closure of the glottis, and the accumulation of large amounts of secretions in the tracheobronchial tree are contributory factors to postoperative pulmonary complications. On the fourth to sixth postoperative day, when the sutures lose some of their effectiveness in holding the wound together, a forceful cough may

produce wound disruption. The clinical effectiveness of E.W.N.P. in preventing and combating postoperative pulmonary complications was accompanied by absence of wound complications, and much less pain than produced by voluntary coughing. The study of the differences in intragastric pressure, which is a reflection of the intra-abdominal pressure[7] during the natural cough with E.W.N.P., offered a reassuring explanation for the advantages of this mechanical method over the natural cough. Since the average peak gastric pressures produced by E.W.N.P. were less than one-third of those produced by the natural cough, and not accompanied by active musculature contraction, stress on the abdominal wound and the consequent production of pain were minimal.

SUMMARY

The effects of Exsufflation With Negative Pressure (E.W.N.P.), a mechanical method of eliminating retained secretions, were studied in respect to cardiovascular function, diaphragmatic motion, and intragastric pressure.

The physiological effects of E.W.N.P. were studied in 17 patients with bronchopulmonary disease with special reference to changes induced on the circulation. Although inspiratory pressures of 40 mm. Hg. were employed to inflate the lungs, the use of a negative lung deflating pressure of 40 mm. Hg. during the expiratory cycle resulted in comparatively low mean ventilatory pressures and, consequently, only slight rises in peripheral venous pressure, i.e., 5.8 cm. H_2O. In contrast, a much higher venous pressure rise took place during the patients' natural vigorous cough, i.e., 16.1 cm. H_2O. Small changes in arterial blood pressure also occurred during E.W.N.P., viz., an average increase of 8 mm. Hg. in systolic and 4 mm. Hg. in diastolic pressure in 22 subjects.

Changes in the electrical axis of the heart due to nearly maximal lung inflation and deflation were similar to those induced by the deepest possible voluntary inspiration and expiration.

Elimination of mucopurulent secretions by E.W.N.P. postoperatively seemed a somewhat safer procedure than the use of the patients' natural cough since intra-abdominal pressure was lower with this procedure: with E.W.N.P., the rise in intragastric pressure averaged 26 mm. Hg. in comparison to a rise of 85 mm. Hg. during the patient's cough. The reduction in pain at the wound site during the use of E.W.N.P. as compared to voluntary cough further suggested its value as a safety factor in respect to healing of abdominal wounds in the postoperative state.

An average rise of 8 mm. Hg. systolic and 4 mm. Hg. diastolic in arterial blood pressure took place in 22 subjects. The change in electrical axis of the heart during the positive and negative pressure cycles were similar to those induced by the deepest possible voluntary inspiration and expiration.

In 17 patients with bronchopulmonary disease and poliomyelitis an average venous pressure rise of 58 mm. H_2O over the control level occurred during E.W.N.P. as compared to that of 161 mm. H_2O in 12 of these

subjects during their own natural cough. The relatively slight rise in blood pressure and venous pressure during E.W.N.P. was related to the low mean mask pressure found in this type of pressure breathing. Higher rises occurred in subjects who resisted inspiratory inflation by the apparatus. In conscious patients, cooperation with the technique of E.W.N.P. is an essential factor in the effective use of this apparatus.

RESUMEN

Se estudiaron los efectos de la exuflación a presión negativa (E.W.N.P.) con un procedimiento mecánico para eliminar las secreciones retenidas y se investigó la función cardiovascular, la movilidad del diafragma y la presión intragástrica.

Se estudiaron los efectos fisiológicos de la E.W.N.P. en 17 enfermos de afecciones bronchopulmonares en especial con relación a los cambios provocados en la circulación. Aunque se emplearon presiones inspiratorias de 40 mm. Hg. para inflar los pulmones, el uso de una presión negativa para desinflar los pulmones, de 40 mm. Hg. durante el ciclo expiratorio produjo presiones medias comparativamente bajas y por consecuencia sólo elevaciones ligeras en la presión venosa periférica como 5.8 cm. H2O.

En contraste hubo un aumento mucho mayor de la presión venosa durante el esfuerzo vigoroso de la tos natural o sea como 16.1 cm. H2O. Ocurrieron también pequeños cambios en la presión arterial durante la E.W.N.P. o sea un término medio de 8 mm. Hg. en la sistólica y 4 mm. Hg. en la diastólica de 22 sujetos.

Los cambios en el eje eléctrico del corazón debidos a una inflación casi maxima y la desinflación fueron similares a los provocados por la inspiración profunda máxima, voluntaria y por la expiración.

La eliminación de secreciones mucopurulentas por la E.W.N.P. postoperatoriamente pareció un procedimiento algo más seguro que el uso de la tos natural de los enfermos puesto que la presión intrabdominal fué más baja con el procedimiento: con la E.W.N.P. la elevación de la presión gastrica fué como media 26 mm. Hg. en comparación con una elevación de 85 mm. Hg. durante la tos del enfermo. La reducción en el dolor en la herida durante el uso de la E.W.N.P. en comparación con la tos voluntaria sugiere además que tiene valor como un factor de seguridad en lo referente a la curación de las heridas abdominales postoperatoriamente.

Una elevación media de 8 mm. Hg. sistólica y 4 mm. Hg. diastólica en la presión arterial ocurrió en 22 sujetos. Los cambios en el eje eléctrico del corazón durante los ciclos de presión positiva y negativa fueron similares a los inducidos por las inspiraciones y expiraciones voluntarias más profundas.

En 17 enfermos con enfermedad bronchopulmonar y poliomielitis la elevación arterial y venosa durante la E.W.N.P. estaba en relación con la media encontrada por la máscara en esta forma de respiración a presión. Ocurrieron elevaciones mayores en los enfermos que resistían a la inflación por el aparato. En los enfermos conscientes la cooperación con la técnica de E.W.N.P. es un factor esencial para el uso efectivo del aparato.

RESUME

Les auteurs étudient les effets de l'exsufflation en pression négative, procédé mécanique qui permet l'évacuation des sécrétions, au point de vue de la fonction cardiovasculaire, du mouvement diaphragmatique et de la pression intragastrique.

Les effets physiologiques de l'exsufflation en pression négative furent étudiés chez 17 malades atteints d'affections bronchopulmonaires en envisageant particulièrement les altérations apportées dans la circulation. Bien que les pressions inspiratoires de 40 mm. de mercure furent utilisées pour gonfler les poumons, une pression négative de désinsufflation de 40 mm. de mercure durant le cycle respiratoire amena des pressions ventilatoires comparativement faibles. Il en résulta des hausses de la pression veineuse périphérique qui restèrent légères: c'est-à-dire atteignirent 5,8 cm. d'eau. A l'opposé, à l'occasion d'un violent accès de toux, on assista à une élévation beaucoup plus grave de la pression eineuse qui atteignit 16,1 cm. d'eau. De petites modifications de la pression artérielle survinrent aussi pendant l'exsufflation en pression négative, une augmentation moyenne de 8 mm. de mercure de la pression systolique et de 4 mm. de mercure de la pression diastolique, chez 22 malades.

Des modifications dans l'axe électrique du coeur, dues à une extension et à une déflation proches du maximum, furent semblables à celles produites par l'inspiration et l'expiration volontaire la plus profonde possible.

L'élimination de sécrétions mucopurulentes par l'exsufflation en pression négative sembla après l'opération être quelque peu plus efficace que le moyen de la toux naturelle des malades, puisque la pression intra-abdominale fut plus faible avec ce procédé: avec l'exsufflation en pression négative, le taux de la pression intragastrique atteignit 26 mm. de mercure, en comparaison du niveau de 85 mm. atteint pendant la toux du malade. Le soulagement de la douleur à l'endroit de la cicatrice pendant l'emploi de l'exsufflation en pression négative, comparée à la toux volontaire, prouve sa valeur comme moyen de secours pour la guérison des blessures abdominales en phase postopératoire.

La moyenne de 8 mm. de mercure en systole, et de 4 mm. en diastole dans la pression sanguine artérielle se vérifia chez 22 malades. Les modifications dans l'axe électrique du coeur pendant le cycle de pressions positives et négatives furent semblables à celles produites pendant l'inspiration et l'expiration volontaire la plus profonde ossible.

Chez 17 malades atteints d'affections bronchopulmonaires et de poliomyélite, le niveau moyen de la pression veineuse pendant l'exsufflation en pression positive, donne les chiffres les plus bas trouvés dans ce type de pression respiratoire. De plus hautes moyennes furent notées chez les sujets qui résistaient à l'inflation inspiratoire par l'appareil. Chez les malades conscients, la coopération à la technique de l'exsufflation en pression négative est un facteur essentiel pour l'efficacité de cette méthode.

ZUSAMMENFASSUNG

Die forcierte Ausatmung mit negativem Druck (hier mit der Abkürzung E.W.N.P. bezeichnet) ist ein mechanisches Verfahren zur Ausscheidung verhaltener Absonderungen, dessen Wirkung auf die Herz-Gefässfunktion, die Zwerchfellbewegung und den Druck innerhalb des Magens untersucht wurden.

Die physiologischen Wirkungen der E.W.N.P. wurden an 17 Patienten mit bronchiopulmonalen Erkrankungen studiert unter besonderer Berücksichtigung der den Blutkreislauf betreffenden Veränderungen. Obgleich zur Aufblasung der Lungen ein Druck von 40 mm Hg angewandt wurde, führte die Verwendung eines negativen Druckes von 40 mm Hg zum Ablassen der Luft aus den Lungen während der Ausatmungsphase zu verhältnismässig niedrigen mittleren Ventilationsdruckwerten und folglich zu nur leichten Anstiegen des peripheren Venendruckes, d.h. 5,8 cm H_2O. Im Gegensatz dazu trat während des natürlichen heftigen Hustens des Kranken ein viel höherer Anstieg des Venendruckes ein, nämlich 16,1 cm H_2O. Es wurden auch geringe Veränderungen des arteriellen Blutdrucks während der E.W.N.P. beobachtet, nämlich (an 22 Versuchspersonen) ein durchschnittlicher Anstieg des systolischen Druckes um 8 mm Hg und des diastolischen um 4 mm Hg.

Die durch die fast maximale Auf- und Abblasung der Lunge hervorgerufenen Veränderungen in der elektrischen Achse des Herzens ähnelten denen, die bei tiefstmöglicher willkürlicher Ein- und Ausatmung zustande kommen.

Die postoperative Ausscheidung schleimig-eitriger Absonderungen vollzieht sich mittels der E.W.N.P. mit geringeren Gefahren als unter der Einwirkung des natürlichen Hustens des Kranken, weil der innere Bauchdruck bei Anwendung der E.W.N.P. niedriger ist: der Anstieg des Druckes im Magen betrug unter Verwendung der E.W.N.P. durchschnittlich 26 mm Hg in Vergleich zu 85 mm Hg während des Hustens. Die Herabsetzung der Schmerzen an der Einschnittsstelle bei Verwendung der E.W.N.P. im Kontrast zu den Erfahrungen mit willkürlichem Hustem ist ein weiterer Hinweis auf den Wert des Verfahrens als Sicherheitsfaktor hinsichtlich der Heilung von Bauchwunden im postoperativen Stadium.

Der bei 17 Kranken mit bronchiopulmonalen Leiden und Poliomyelitis beobachtete durchschnittliche Anstieg des Blutdrucks und des Venendruckes während der E.W.N.P. wurde zu dem niedrigen mittleren Maskendruck, der bei dieser Form der Druckatmung beobachtet wird, in Beziehung gebracht. Höhere Anstiege des Druckes traten bei Personen auf, die der Aufblasung der Lungen durch den Apparat Widerstand entgegensetzten. Bei Kranken mit erhaltenem Bewusstsein spielt die freiwillige Mitarbeit an der technischen Durchführung der E.W.N.P. eine wesentliche Rolle in der wirksamen Anwendung des Apparates.

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Tuberculosis of the Myocardium
A Case Report

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During the past several years many instances of myocardial tuberculosis have been reported. In 1950, Diefenbach,[1] reviewing then available material, reported an incidence of 0.28 per cent of myocardial involvment in 10,000 autopsied cases of tuberculosis. The types of involvement include miliary, which made up the smaller number of cases, and nodular which was the usual form; the pericardium was regularly involved in the later type.

The infective process is thought to reach the myocardium by: (a) hematogenous dispersion, (b) lymphatic spread, or (c) direct extension from the pericardium. The pericardium over the right auricle, because of its close adjacence to involve bronchial lymph nodes, appears the favorite initial site of invasion.

A case is here reported which we believe has unusual features.

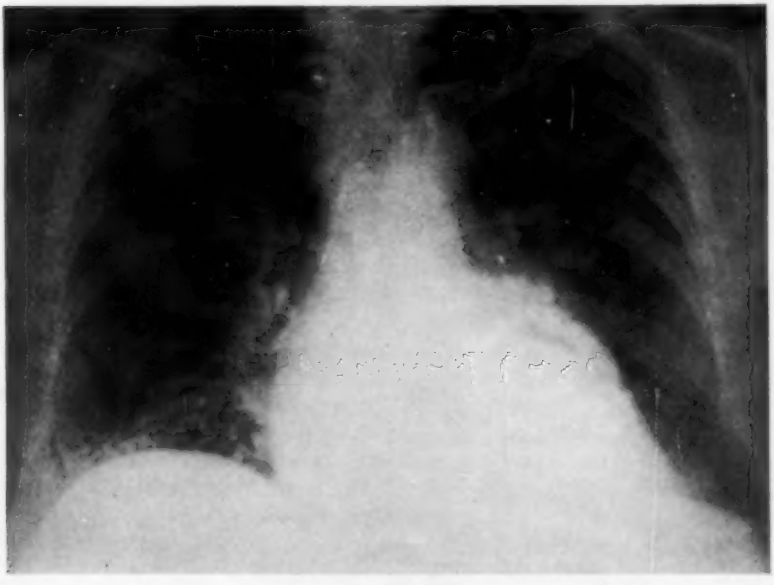

FIGURE 1: Postero anterior roentgenogram of chest made in 1952.

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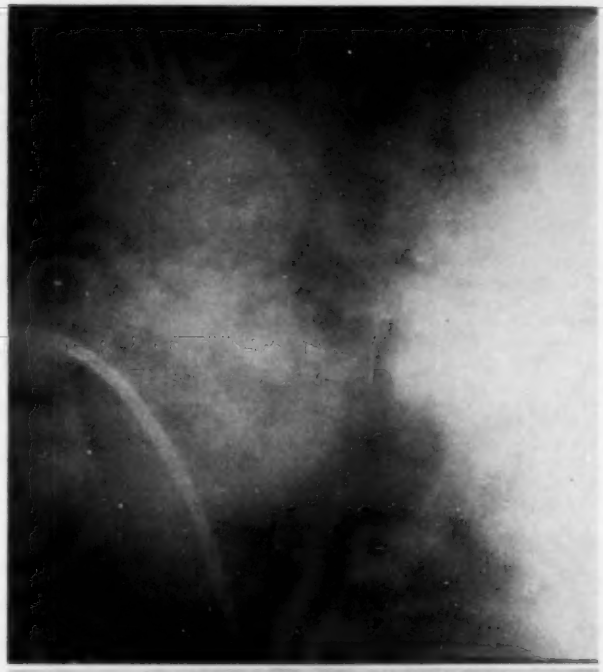

FIGURE 3

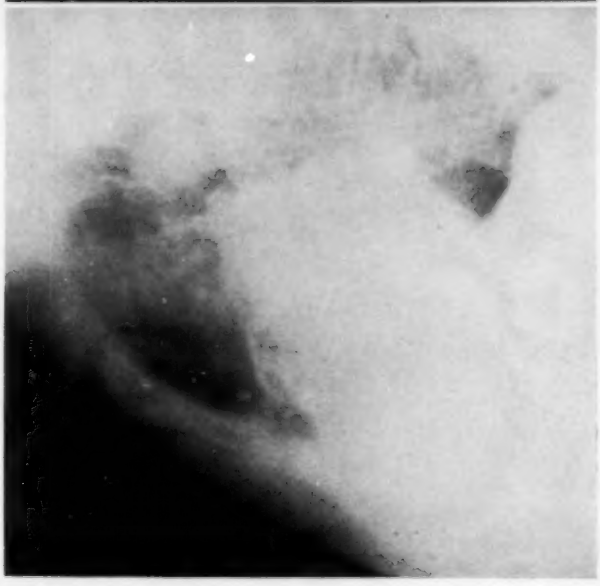

FIGURE 2

Figure 2: Left lateral roentgenogram of chest made in 1952.—*Figure 3:* Flat film of abdomen made during terminal illness showing calcified areas in heart shadow.

Past Clinical Data

Mrs. J. M., age 52, was a white, well nourished mother of four living, healthy children. There was no family or personal history of known tuberculosis. She had appendectomy in 1932 and cholecystectomy in 1937. She was hospitalized in 1944 for treatment of a "heart condition" (later ascertained by repeated electrocardiograms to represent "extensive myocardial damage with evidence of posterior infarction").

In 1945, she was treated for "angina pectoris" and in 1952, she was hospitalized briefly for an acute upper respiratory infection. Electrocardiograms then studied were said to show "no significant change from those made in 1944 and 1945." The hospital history records the presence at that time of "grade II mitral systolic murmur, transmitted to the left axilla."

A roentgenogram of the chest, in 1952, was interpreted as follows: "The heart is spherical in contour; otherwise the heart and aorta are normal. The posterior mediastinum is clear. There is a residual of an old pleural pulmonary reaction along the left superior anterior margin of the heart, with some mottled calcific deposit here. This does not appear to be of recent origin, and no recent pulmonary disease is detected. The diaphragms are regular, and there is no effusion. Conclusion: Essentially negative examination." Figures 1 and 2.

Immediate Clinical History

During the night of January 12, 1954, her husband discovered her lying helplessly on the bathroom floor, confused, incoherent and unable to raise her right arm and right leg. Physical examination, after hospital admittance a short time later, confirmed the presence of complete right hemiplegia. Her blood pressure was 112/60, pulse 120 plus, irregular in volume and rhythm, temperature 98 and respirations 20. A few basal rales were elicited. The heart was grossly enlarged and harsh systolic and diastolic murmurs were heard over the entire precordium and into the left axilla. Nothing noteworthy was found in examination of the eyes, ears, nose and throat.

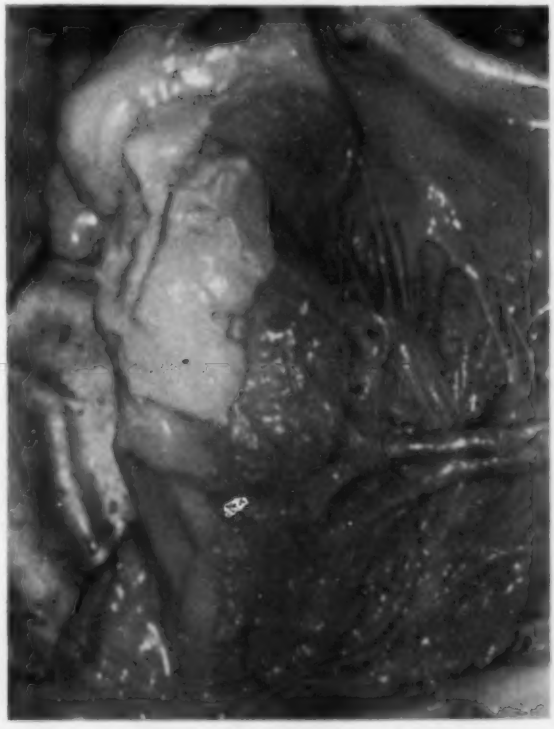

FIGURE 4: The heart showing caseous and partly calcified abscess of myocardium.

Neck rigidity was not present. Reflexes were unchanged except they were markedly exaggerated in the right arm and right leg. Laboratory tests were not diagnostically helpful. Spinal puncture was not done. Electrocardiogram indicated "tachycardia, auricular fibrillation and old posterior coronary infarction." Blood cultures were negative.

On the basis of such history and physical findings, a presumptive diagnosis was made of thrombo-embolic phenomena secondary to auricular fibrillation and treatment was instituted accordingly. Heparin was given; digitalization begun; quinidine and a rigid rest regimen maintained.

The immediate response to treatment was encouraging. Within a few hours, sensorium had cleared and evidence of the right hemiplegia was beginning to disappear. Reflexes were still exaggerated on the right side. She was comfortable and cheerful. Her appetite was good. Cardiac arrythmia persisted although pulse rate was reduced to about 80. The outlook had definitely improved and cautious optimism seemed justified.

Quite suddenly, during the morning of January 24, 1954, she began vomiting and complained of severe upper abdominal pain. Neither morphine nor aminophylline adequately relieved her. Gaseous distention developed and with this a decrease in bowel sounds. Fair relief was finally obtained after two or three hours, by oxygen (tent) and the use of Levine suction. Distention was reduced, bowel sounds were again heard and she said she felt improved. During this interval, a flat film of the abdomen was taken which was described by the roentgenologist as follows: (Figure 3)

"No gas filled distended small bowel was identified. An opaque tube down the lower thoracic spine area turns to the left presumably in the esophagus and stomach. No other unusual findings are noted in this examination of the abdomen. At the level of the left diaphragm, near midline, in a continuation of the cardiac silhouette, there is a mottled, rather dense calcium deposit. This may possibly be a concentration of calcium deposit in the pericardium. No unusual calcific shadows are observed either above or below the diaphragm on this single film."

Her condition remained critical. She became increasingly restless until she finally lapsed into deep unconsciousness. Right hemiplegia returned, cyanosis developed and death occurred that afternoon, January 25, 1954.

The autopsy report contains the following.

Autopsy performed January 26, 1954. The body is that of a well developed, rather obese, middle-aged, white female, appearing older than the stated age of 52. Excess fluid in either pleural space is absent; the lungs are focally atelectatic. There is a dense, left, apical pulmonary scar present, which probably represents a reinfection type tuberculosis in the past. There is no gross evidence of pneumonia. There are no mediastinal masses.

The heart is markedly enlarged, and the pericardium is densely adherent to the visceral pericardium by multiple mass of calcified placks. It is necessary to remove the pericardial sac with the heart, and so dense are these adhesions that the pericardial sac proper can only be regionally freed from the underlying visceral pericardium. The heart proper weighs an estimated 450 grs.; this is due to eccentric hypertrophy of the left ventricle of hypertensive type. The myocardium of both the left and the right ventricles is the site of massive calcific infiltrate, and the coronary vessels are the sites of rather advanced segmental atherosclerosis and in some areas, this is calcific. A thrombus is not demonstrated, however, and there are no areas of recent softening or old scar in the myocardium upon repeated section. Both atria are free of thrombi, but the left ventricle contains a quantity of pasty, putty-like material which originates in a cold abscess of the myocardium, which has ruptured into the left ventricle. Valvular deformities are lacking, and the coronary ostia are patent. The aorta contains a number of non-ulcerated atheromatous placks. Adherent to the pericardial sac, in its posterior portion, is a calcified lymph node which presumably is the route of the original infection of this pericardium. (Figure 4)

Microscopic Examination

Sections of the heart following decalcification reveal wide spread calcification alternating with areas of caseation and fibrosis. Occasional Langhans' type foreign body giant cells are encountered, but these are rare. Associated with the calcification and caseation are areas of lymphocytic infiltrate. No epithelioid cell elements can be identified. The material from the left ventricle consists solely of caseous debris. Smears made of the caseous material reveal a rare acid fast organism with a characteristic of Mycobacterium tuberculosis. After 8 week incubation, cultures of the caseous material from the myocardium revealed cake-crumb colonies typical of *Mycobacterium tuberculosis*, both grossly and upon microscopic examination.

Gross anatomical diagnosis:

1. Advanced calcific constricted pericarditis (healed tuberculous pericarditis).
2. Cold abscess of the left ventricle (intramural).

3. Terminal rupture of the foregoing abscess into the left ventricle.
4. Multiple cerebral emboli (clinical).
5. Focal atelectasis of both lungs.
6. Terminal congestion and edema of both lungs.
7. Surgically missing gallbladder.
8. Ancient cholecystectomy scar.
9. Healed reinfection type tuberculosis (left upper lung lobe).
10. Old calcified lymph node adherent to pericardial sac.
11. Obesity.
12. Senile change involving the skin and appendages.

SUMMARY

During the past decade, tuberculosis of the myocardium has been somewhat frequently reported. So far as we know, it has been described as occurring mainly in cases of far advanced pulmonary or generalized tuberculosis.[2, 3, 4, 5, 6] In the case presented here, tuberculosis had not been previously diagnosed and no focus of active tuberculosis, other than in the myocardium, was found at the time of death. In reviewing the past history, it appears conceivable that pericardial invasion took place in 1944. As calcification progressed over the years, there developed electrocardiographic changes characteristic of myocardial infarction. Myocardial infarction was not found at autopsy; instead a large tuberculosis abscess was present in the wall of the LEFT ventricle. This had recently ruptured into the cavity of the left ventricle causing embolic phenomena, including cerebrovascular involvement and early death. Diagnosis was substantiated by autopsy, microscopic tissue study and successful growth of typical Mycobacterium tuberculosis from the caseous material obtained at the autopsy.

RESUMEN

Durante los últimos diez años se han referido casos de tuberculosis del miocardio con alguna frecuencia. Hasta donde conecemos se han descrito que ocurren principalmente en casos de tuberculosis muy avanzada o generalizada.[2, 3, 4, 5, 6]

En el caso aquí presentado no se había diagnosticado, foco activo de tuberculosis fuera del miocardio ni se encontró hasta la muerte. Revisando su historia parece posible que la invasión pericárdica tuvo lugar en 1944.

A medida que la calcificación progresó por años, se presentaron cambios característicos de infarto del miocardio. No se encontró infarto del miocardio a la autopsia; en su lugar había un gran absceso tuberculoso en la pared del ventrículo izquierdo. Este habíase abierto hacia la vacidad del ventrículo izquierdo do cuasando fenómenos embólicos incluyendo compromiso cerebrovascular y muerte pronta.

El diagnóstico fué confirmado a la autopsia, con estudio microscópico de tejidos y cultivo de bacilo tuberculoso del material caseoso obtenido a la autopsia.

RESUME

Depuis 10 ans, la tuberculose du myocarde a été assez souvent rapportée. A la connaissance des auteurs, elle a été principalement décrite dans les cas de tuberculose pulmonaire avancée ou généralisée. Dans l'observation rapportée, la tuberculose n'avait pas été antérieurement diagnostiquée et

aucun foyer de tuberculose active autre que celui du myocarde n'a été trouvé au moment du décès. En revoyant les antécédents, il parait probable que le péricarde avait été atteint en 1944. Comme les lésions se calcifiaient progressivement au cours des années, elles amenèrent les modifications électrocardiographiques généralement caractéristiques de l'infarctus myocardique. Au lieu de l'infarctus que l'on attendait à l'autopsie, on trouva un volumineux abcès tuberculeux dans la paroi du ventricule gauche. Il venait de se rompre dans la cavité du ventricule gauche, provoquant des phénomènes emboliques qui avaient entrainé une atteinte cérébro-vasculaire et la mort rapide. Le diagnostic fut aidé par l'autopsie, l'étude microscopique des tissus et la culture des bacilles de Koch à partir d'éléments caséeux prélevés à l'autopsie.

ZUSAMMENFASSUNG

Im letzten Jahrzehnt wurde des öfteren über die Tuberkulose des Myokards berichtet. Unseres Wissens wurde das Vorkommen dieser Erkrankung hauptsächlich bei Fällen mit weit fortgeschrittener Lungentuberkulose oder generalisierter Tuberkulose beschrieben.[2, 3, 4, 5, 6]

Bie dem hier vorgelegten Fall wurde früher keine Tuberkulose diagnostiziert, und es wurde nach dem Tode des Patienten kein Herd einer aktiven Tuberkulose ausserhalb des Myokards gefunden. Unter Berücksichtigung der Vorgeschichte ist anzunehmen, dass 1955 das Perikard befallen wurde. Bei zunehmender Kalzifizierung im Laufe der Jahre kam es zur Ausbildung elektrokardiographischer Veränderungen im Sinne eines Herzinfarktes. Bei der Autospie wurde jedoch kein Herzinfarkt gefunden, sondern ein grosser tuberkulöser Abszess in der Wand des linken Ventrikels.

Dieser Abszess war kurz vorher in den linken Ventrikel perforiert, worauf es zu embolischen Erscheinungen einschliesslich zerebraler Symptome und zum Exitus kam. Die Diagnose wurde durch Autopsie, histologische Untersuchung und kulturellen Nachweis von Tuberkulbakterien aus dem käsigen Material gesichert.

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The Surgery of Patent Ductus Arteriosus*

A Report of the Section on Cardiovascular Surgery

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Burwell[1] has likened patent ductus arteriosus to a time bomb with a long fuse, pointing out that it is neither a harmless nor a well-borne lesion. Shapiro and Keys[2] state that 80 per cent of patients with this congenital defect will succumb to the lesion, and that those alive at 17 die at an average age of 35. The potential hazards of an uncorrected patent ductus, acting as Holman, Gerbode and Purdy[3] have pointed out like a large arterio-venous fistula, are 1) retardation in physical and perhaps mental development, 2) cardiac dilatation and decompensation, 3) subacute bacterial endarteritis, 4) pulmonary hypertension with its resultant pulmonary vascular changes, and 5) rarely, rupture of a dilated pulmonary artery.

Material

Since Gross,[4] in 1939, demonstrated that surgical interruption of the ductus was feasible, a large number of such procedures have been performed. The Subcommittee on Cardiovascular Surgery of the American College of Chest Physicians felt that the collection of a statistically significant number of these operations would provide valuable information for the medical cardiologist, the cardiovascular surgeon, the pediatrician, and the general practitioner alike. Interruption of the ductus was elected as the first of an annual series of cardiovascular operations to be analyzed because it was the principal wedge in the surgery of cardiac lesions and thus has been in use a longer time, and because a large volume of data could be assembled from reliable surgical sources. Only patent ductus arteriosus cases without any other congenital malformations were included. Utilizing the large Advisory Committee, herein listed, of outstanding cardiovascular surgeons in this country and abroad, a total of 4,448 operative cases was collected from 49 collaborators. The analysis of these cases comprises the body of this report, and is purposely given in concise form.

Of the 4,448 cases, 552 were eliminated because of insufficient data in the return questionnaires, leaving a total of 3,896 fulfilling the rigid criteria imposed by the committee. Of these, 2,929 operations were performed in children and 967 in adults. Only patients 14 years of age or under were included in the children's group.

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**Chairman, Section on Cardiovascular Surgery, American College of Chest Physicians.

TABLE I
SYMPTOMATOLOGY PREOPERATIVELY

Total No.	None No.	None Per Cent	Myocardial Insufficiency No.	Myocardial Insufficiency Per Cent	Infection No.	Infection Per Cent
Children (up to 14 yrs.) 2,077	1,436	(69.1)	570	(27.4)	71	(3.5)
Adults 829	402	(48.5)	338	(40.8)	89	(10.7)

Preoperative Symptomatology

Table I shows the incidence of the two most significant preoperative symptoms, myocardial insufficiency and infection, in the cases on which full data was given in this category. Of the children, 69.1 per cent had no symptomatology in contrast to only 48.5 per cent of the adults. In the children's group, 27.4 per cent had myocardial insufficiency. This figure rose to 40.8 per cent in adults. Infection was present in 3.5 per cent of the children and in the much larger figure of 10.7 per cent of the adults. The sharp upswing in both myocardial insufficiency and infection as age increases seems to emphasize the statement of Burwell previously quoted. Obviously patent ductus arteriosus is not an innocuous lesion.

Mortality

Table II summarizes the mortality and the results in both adults and children undergoing surgery. As to mortality, in the children's group 2.3 per cent were considered operative deaths. In the adults this figure rose to 5.5 per cent. The overall initial mortality of the 3,896 cases was 2.77 per cent. Figures on the late mortality, while exceedingly low, were not considered statistically significant because of the incomplete follow-up in many cases. The increasing risk of carrying an unoperated ductus is obvious, with the mortality more than doubling in the adult group.

Clinical Results

The clinical result in the survivors was considered satisfactory in 98.3 per cent of the children and 95.5 per cent of the adults. Unsatisfactory results were obtained in 1.7 per cent of the children and 4.5 per cent of the

TABLE II

MORTALITY					CLINICAL RESULT				
Initial			By 5 Yrs.	By 10 Yrs.		Satisfactory		Unsatisfactory	
Children	No.	Per Cent			Children	No.	Per Cent	No.	Per Cent
2,929	67	(2.3)	18 (not computed, too few to be significant)	2	2,832	2,784	(98.3)	48	(1.7)
Adults					Adults				
967	53	(5.5)	4 (not computed, too few to be significant)	1	902	861	(95.5)	41	(4.5)

adults. Although the results from surgical intervention thus seem excellent at any age, the argument for operation in childhood is further enforced.

Specific Problems in Patent Ductus Surgery

In addition to the foregoing information, the co-operating surgeons were asked four questions of particular interest. These were: 1. Do you now favor ductal ligation or division? 2. Do you favor ductal interruption in the presence of pulmonary hypertension up to 90 mm. systolic? 3. Do you favor ductal interruption in the presence of clear-cut reversal of the shunt? and 4. Do you favor ductal interruption in the absence of cardiac enlargement or clinical symptomatology?

Surgical Technique

Twenty-eight (57.3 per cent) of the investigators favored division of the duct as opposed to 16 (32.7 per cent), who preferred the ligation technique. Three of the 49 answering the questionnaire individualized on division and ligation, and two did not answer.

Interestingly, there was little difference in the mortality between the ligated and the divided series. For example, of the 1,123 children operated upon by ligation technique, 23 died giving a mortality of 2 per cent. Of the 1,659 children in which the duct was divided, 34 succumbed yielding an almost identical mortality of 2.1 per cent. Three hundred and fifty-three adult patients had their ductus ligated. Of these 15 (4.3 per cent) died. Twenty-nine (5.2 per cent) of the 553 adults operated upon by division techniques were listed in the initial mortality figures. These figures are shown in Table III.

TABLE III
COMPARISON OF MORTALITY
Ligation versus Division

Children—2,929 Cases			
Technique	Cases	Initial Mortality No.	Per Cent
Ligation	1,123	23	(2.0)
Division	1,659	34	(2.1)
Unspecified	147	3	
Adults—967 Cases			
Technique	Cases	Initial Mortality No.	Per Cent
Ligation	353	15	(4.3)
Division	553	29	(5.2)
Unspecified	61	3	

TABLE IV
OVERALL COMPARISON OF MORTALITY
Ligation versus Division

Technique	Cases	Initial Mortality No.	Per Cent
Ligation	1,476	38	(2.6)
Division	2,212	63	(2.8)

TABLE V
ANALYSIS OF DEATHS

23 Reports—1,650 Cases

Operative (Hospital) Causes of Death		Late Causes of Death	
Hemorrhage at operation	29	Congestive heart failure	2
Cardiac asystole	6		
Ventricular fibrillation	1	Persistent infection of blood stream	3
Embolization	1		
Pulmonary edema	2	Pulmonary infarction	0
Cerebral hemorrhage	2		
Hyperpyrexia	2		
Unknown	1		
TOTAL	44	TOTAL	5

The overall mortality of children and adults of the cases ligated was 2.6 per cent, and of the cases divided 2.8 per cent, as summarized in Table IV. The principal argument advanced for the ligation technique has been the greater safety of the procedure. The close approximation of the mortality figures in the two techniques would not appear to indicate the validity of this contention.

Pulmonary Hypertension

In regard to ductal interruption in the presence of pulmonary hypertension, 37 surgeons of the 49 replied it should be done, many making the reservation that no right-to-left shunt be present. Only two were opposed to ductal interruption, while 10 did not commit themselves. With more and more cases of atypical patent ductus showing pulmonary hypertension being discovered, the predominance of affirmative opinion is significant.

Reversal of Shunt

When the shunt has reversed from a predominantly left-to-right flow to a right-to-left one, only eight surgeons felt the duct should be interrupted. All of them made the reservation that only temporary clamping be done, and that if the pulmonary artery pressure then fell, the duct should be divided. If, on the other hand, an increase in pulmonary pressure resulted, the duct should not be interrupted. Thirty-one were opposed to any interruption in the presence of clear-cut reversal of shunt, and 10 did not answer. This predominant opposition to ductal interruption would support the conclusions of Ellis, Kirklin, Callahan and Wood[5] who reviewed the reported cases of ductal interruption in the face of a right-to-left shunt and found a mortality of 56 per cent in the 18 collected cases. Of their own 14 patients having this condition the mortality rate was 50 per cent. In 16 additional cases of marked pulmonary hypertension without reversal of shunt there were no deaths.

Absence of Cardiac Enlargement and Symptomatology

All but one of the surgeons contributing to the report favored ductal interruption in the absence of cardiac enlargement or clinical symptomatology, although three of the 48 answering "yes" specified that this applied to children but not to adults. Obviously the ultimate grave dangers inherent in unoperated ductus far outweigh the risk of surgery in the opinion of the great majority of cardiac surgeons.

Supplemental Material

All of the foregoing information was obtained from the simplified questionnaire. Additional information was requested and was obtained from a limited number of the co-operating group. These questions were in regard to changes in heart size, catheterization findings, coexistent aneurysm, detailed analysis of deaths, and associated findings such as pulmonary vascular changes, sclerosis, and electrocardiographic changes.

Heart Size

A sufficient number, 954 cases, was reported as to preoperative heart size to be significant. Of these 219, (22.9 per cent) were greatly enlarged, 349 (36.6 per cent) were slightly enlarged, and 386 (40.5 per cent) were within normal limits. Five hundred and sixty-two cases were reported giving the size of the heart postoperatively. Of these, 107 (19 per cent) remained enlarged above normal, 280 (49.8 per cent) were reduced to normal size and 175 (31.2 per cent) were smaller than the preoperative size.

Catheterization

The catheterization data was not felt to be statistically significant because it came from a relatively limited group of investigators.

Coexistent Aneurysm

Seventeen surgeons, representing 1,043 cases, reported eight coexistent aneurysms of the ductus, 35 of the pulmonary artery, and 31 of the aorta. This would represent an incidence of 7.1 per cent, and would seem to be a finding of considerable importance.

Analysis of Deaths

Deaths were reported in detail in a group representing 1,650 cases reported by 23 different surgeons. There were 45 hospital deaths and five late deaths, as listed in Table V. Of the first group, 29 deaths were from hemorrhage at operation, by far the largest single cause. Cardiac arrest accounted for six more deaths. The other nine are listed in the table. Of the five late deaths, two were from congestive heart failure and three from persistent infection of the blood stream.

Hemorrhage at operation obviously is the major danger in the procedure. Although the figures are probably too small to be entirely valid statistically, there was a slightly higher incidence of hemorrhage in the

patients operated upon with ligation technique than in the group having division. If such is true, ligation is not a safer procedure than division.

DISCUSSION AND CONCLUSIONS

The committee feels that the analysis of as large a group of cases as this has produced significant data, particularly in view of the reliability of the source of the material. The 3,896 cases reported by the 49 co-operating surgeons actually represents a group operated upon by a considerably larger number of individuals than the 49, thus providing a representative cross-section of well-supervised surgery. It is hoped that the data presented will serve to emphasize the excellent authoritative reports already published from single clinics, and help to resolve any misconceptions about the fundamental worth of patent ductus surgery that may persist in the minds of those not closely conversant with the field.

If conclusions are to be drawn, it can be stated that the operation is a fairly well standardized procedure with two techniques of ligation and division, both carrying comparably low mortalities. Although the majority of surgeons favor division rather than ligation, it should be emphasized that the technique in which the operator has been best trained is usually the safest procedure in his hands.

The clinical results are so predominantly good in both children and adults, that there can be little question concerning the efficacy of the procedure. Because the mortality is significantly lower in children, and the final result better, early operation in childhood is definitely preferable. The optimal age reported in the literature, but not given in this report, is generally agreed to be from three or four years up to 15 or 20. Between six and 12 would seem to be ideal. Should signs of failure appear prior to this time, infants and younger children should be operated upon without delay. In the older individual, particularly in the 40's or 50's, careful individual consideration must be made. Catheterization studies are often of considerable value, particularly if pulmonary hypertension is suspected. Such atypical ductus cases demand careful investigation.

Surgical closure of the ductus appears hazardous and probably unwise in patients in whom there is demonstrated preoperatively a right-to-left shunt that exceeds in magnitude the left-to-right shunt. It would also seem desirable to avoid surgical closure of the ductus if a rise in pulmonary arterial pressure and a fall in systemic pressure occur in response to ductal occlusion at the time of operation.

Lastly it can be stated that the predominant opinion of competent surgical authority favors ductal interruption in all cases which have no other congenital malformation and in whom there is absence of cardiac enlargement or clinical symptomatology. The mere presence, then, of a patent ductus is indication for surgery in any child and in most adults, with the qualification that careful investigation and individualization be done. The mortality is low, and the results excellent.

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The President's Page

The year 1956 promises to be an exciting one for the College, with many important meetings, a Congress in Germany, post-convention tours, and other planned activities. I trust that all College members will participate in some or all of these scientific assemblies.

In Boston in November, we had a fine meeting and I want to congratulate the New England States Chapter of the College for their splendid hospitality.

In these monthly messages, I plan to keep the members of the College informed concerning our varied activities. The reports of our councils, committees, and sub-committees which are actively engaged in carrying on worthwhile projects should be of interest to all of us who are devoting our practice to pulmonary or cardiovascular problems.

In the November issue of the journal, we published a report of the Council on Public Health. Requests have been received for thousands of reprints of this excellent report. A report of the Committee on Bronchoesophagology, entitled "Problems in the Training of Bronchoesophagologists," appeared in the December issue. In this issue, you will find the first report of the study being made by the Section on Cardiovascular Surgery of the Committee on Cardiovascular Disease. There is also an interesting report from the Committee on College Chapters.

I would like to point out that the Committee on Resident Fellowships has placed eight young physicians from other countries during the past year and hopes to be able to increase this number in 1956. These resident fellows are carefully selected by the committee and their knowledge of the English language is vouched for by the American Consulates in their respective countries. It would be helpful if you who are in a position to take a resident for a year or more of training in thoracic or cardiovascular surgery, or in clinical cardiovascular or pulmonary disease, would advise the committee, as there are now many applicants who could be placed if facilities permitted.

Commencing with the January, 1956 issue, Section XV of "Excerpta Medica," the title of which was previously known as "Tuberculosis and Pulmonary Disease" will be changed to "Chest Diseases." This well-known, worldwide abstract service, published in Amsterdam, will be under the sponsorship of the American College of Chest Physicians. The Editorial Board has been revised to include some of the outstanding authorities in the world and it is hoped that every member of the College will subscribe to this excellent abstract service.

The membership of the College showed a healthy increase during the past year, as you have probably noted from the number of names appearing in the Roster of Candidates. It might be well to point out that the mere fact that a physician's name appears in the Roster of Candidates does not mean that he has been accepted for membership, nor that he will be approved for the type of membership for which he is applying. In accordance with the College Bylaws, this Roster is printed biannually and is sent to every member of record in order that they may register their approval or disapproval of any candidate whose name appears. The opinions of our members are very helpful in evaluating an applicant's qualifications, and recommendations and objections are always appreciated. After the publication of the names in the Roster of Candidates, the applications are reviewed by the Governors and Regents in the candidates' states and are then presented to the Chairman of the Board of Regents for final consideration, with all recommendations from members, Governors, and Regents. Through this procedure, the entire membership of the College has a part in the selection of new members, and it is for this reason that every member should carefully review the names appearing in each Roster of Candidates and comment upon those whom he knows personally.

In future issues of the journal, I expect to discuss some of our other activities in an effort to keep you advised of what the College is doing.

James H. Stygall

FOURTH INTERNATIONAL CONGRESS

The Cathedral of Cologne

Physicians in all parts of the world have expressed interest in attending the Fourth International Congress on Diseases of the Chest, to be held in Cologne, Germany, August 19-23, 1956, From present indications, it appears that the attendance at this Congress will exceed the 2500 registered at the Barcelona Congress in 1954. Many requests for places on the scientific program have been received. The chairman, Dr. Andrew L. Banyai, with the members of his committee and with the cooperation of the Executive Committee in Germany, is giving serious study to the organization of an outstanding program for presentation in Cologne.

The city of Cologne and the Government officials in West Germany are making elaborate plans for the entertainment of the delegates who will attend the Fourth International Congress on Diseases of the Chest.

There is great demand for hotel rooms and accommodations in pensions for the Congress. Requests for accommodations are being handled in the order received at the Executive Offices of the College in Chicago. A Secretariat has been established in Cologne to assist in the housing of physicians and their families. Confirmations of hotel and other accommodations will be sent directly from the Secretariat in Cologne.

The Executive Committee for the Congress, under the chairmanship of Prof. Joachin Hein, Regent of the College for Germany, and the Vice President of the Congress, Prof. H. W. Knipping, Governor for Nordrhien-Westfalen, are in charge of the arrangements for the Congress and are concentrating their efforts in this direction.

The following post-convention tour has been planned: The Delegates and their families will leave Cologne on Friday, August 24, and visit the cities of Wiesbaden, Baden Baden, Munich and Vienna. The tour will include a boat trip up the Rhine River, a visit to the University City of Heidelberg, as well as receptions and scientific programs in the cities to be visited. In Vienna, the Delegates will have the opportunity to attend the Congress of the International Bronchoesophagological Society, August 31-September 2, in addition to touring this historical city and attending a performance at its world famous opera house. A limited number of tickets for the opera have been reserved and will be issued in the order that requests are received.

Physicians in the United States and Canada desiring to participate in the post-convention tour should contact International Travel Service, Inc., Palmer House, Chicago, Illinois.

22nd ANNUAL MEETING PROGRAM IN PREPARATION

The Committee on Scientific Program, under the chairmanship of Dr. William A. Hudson, is working diligently in the organization of the scientific program to be presented at the 22nd Annual Meeting of the College, Hotel Sherman, Chicago, Illinois, June 7-10, 1956. Dr. Hudson has announced that the program will be available for publication in an early issue of *Diseases of the Chest*.

The following themes are being developed to be presented by prominent speakers with extensive experience in these fields:

"The Present Status of our Knowledge Concerning Cancer of the Lung"
"Cardiovascular and Pulmonary Physiology with Clinical Applications"
"Diagnosis and Treatment of Cardiovascular and Pulmonary Disturbances" (medical and surgical, including asthma, emphysema, bronchiectasis, coronary disease, pulmonary and cardiac function)
"Cardiovascular Surgery" (basic principles and particular conditions)
"Tuberculosis and Related Pulmonary Conditions"
"Environmental and Occupational Influences"

A number of panel discussions will be presented on the above subjects and a sufficient amount of time will be allotted to discussion from the floor. There will also be a diagnostic-treatment conference and a special session entitled "The Roving Reporter" which will present brief reports on recent research in pulmonary and cardiovascular diseases.

The Fireside Conferences, which were introduced at the 21st Annual Meeting in Atlantic City last June, will be repeated by popular demand on Friday evening, June 9. Photographs taken at the Fireside Conferences held in Atlantic City appear on the next page and illustrate the enthusiasm and interest with which these sessions were received. For the enlightenment of members who had not the opportunity to attend the sessions last year, we wish to point out that more than thirty subjects were discussed, covering a range of almost every conceivable aspect of chest disease, with an outstanding scientist leading the discussion of each subject. Refreshments were available to assist in keeping the discussions going at the various tables. The same procedure will be followed in the Fireside Conferences to be presented at the 22nd Annual Meeting.

The round table luncheon discussions, which have become an integral part of our annual meeting programs, will be presented on each of the three days of the meeting, Friday, Saturday and Sunday, June 8-10. Motion picture sessions on diseases of the chest will be presented concurrently with the scientific session. The first "Louis Mark Memorial Lecture" will be presented on the opening night of the meeting, Thursday, June 7, by a prominent physician.

(Chicago Park District Photo)

Chicago Skyline

FIRESIDE CONFERENCES
21st Annual Meeting, American College of Chest Physicians
Ambassador Hotel, Atlantic City, New Jersey, June 2-5, 1955

Examinations for Fellowship in the College will be held on Thursday, June 7. The annual Seminars, which have been accredited by the Board of Examiners for candidates for Fellowship in the College, will be presented on Wednesday, June 6.

Meetings of all councils and committees of the College will be scheduled for Thursday, June 7, at the Hotel Sherman. Members of the College councils and committees are urgently requested to make plans to attend these important meetings.

Honorary Fellowship in the College will be conferred upon prominent scientists at the annual Convocation to be held on Saturday evening, June 9. This will be followed by a cocktail party and the Annual Presidents' Banquet. There will be no speeches, just music, mirth and good fellowship.

Mrs. Otto L. Bettag, Chicago, Chairman of the Ladies Reception Committee, has announced that an enjoyable program of events is being planned for the ladies.

A hotel reservation form may be found on page xxii of this issue of the journal and it is suggested that this form be mailed at once to the Hotel Sherman. Reservations will be accepted in the order received and it is advisable that requests be mailed immediately to be assured of accommodations. The American Medical Association will meet in Chicago, June 11-15, 1956. When completing the hotel reservation form, please give arrival and departure dates.

REPORT OF COMMITTEE ON COLLEGE CHAPTERS

In reviewing the progress made by our College chapters in the United States during the past year, it is a pleasure to report that 29 of our 30 domestic chapters held scientific sessions and that some of the chapters have adopted the plan of having several meetings each year. The attendance at most of the 1955 meetings showed an appreciable increase over the 1954 meetings and it is interesting to note that those chapters which met in connection with their state medical society had the largest attendance. The following report covers the period from January 1, 1955 to date.

CHAPTER	LOCATION	DATE	ATTENDANCE
Alabama	Montgomery	April 20	37—Total
Arizona	Tucson	May 7	42—(15 members, 27 guests)
Arkansas	Hot Springs	May 30	12—Total
California	San Francisco	April 30	Over 100
Colorado	Denver	September 24	65—(31 members, 34 guests)
Florida	St. Petersburg	April 3	52—(22 members, 30 guests)
Georgia	Augusta	May 3	50—Total
Illinois	Chicago	May 18 (Annual)	73—(43 members, 30 guests)
Indiana	French Lick Springs	October 18	29—(15 members, 14 guests)
Kansas	Hutchinson	May 5	102—(22 members, 80 guests)
Kentucky	Louisville	September 29	No record of attendance
Michigan	Detroit	3 Meetings	No record of attendance
Minnesota	Minneapolis	May 23	No record of attendance
Mississippi	Biloxi	May 9	19—(13 members, 6 guests)
Missouri	Kansas City	March 27	No record of attendance
New England	Boston	4 Meetings	All well attended
New Jersey	Atlantic City	April 18	Approximately 85
New York	Buffalo	May 12 (Annual)	40—Total
	New York City	Feb. 17 (Clinical Session)	150—Total
North Carolina	Oteen	October 7	66—(9 members, 57 guests)
Ohio	Cincinnati	April 20	Approximately 50
Oklahoma	Tulsa	May 8	19—(11 members, 8 guests)
Pacific Northwest	Vancouver	Nov. 4 & 5	74—Total
Pennsylvania	Pittsburgh	June 3	96—(40 members, 56 guests)
Potomac	White Sulphur Springs, W. Va.	October 7	42—Total
Southern	Houston, Texas	Nov. 13 & 14	82—Total
Tennessee	Nashville	April 12	24—(11 members, 13 guests)
Texas	Ft. Worth	April 24	No attendance record
Virginia	Richmond	October 16	58—(33 members, 25 guests)
Wisconsin	Milwaukee	May 1	50—Total

The Illinois Chapter held a special scientific meeting at which Prof. L. D. Eerland, Groningen, Holland, Regent for the College in Holland, lectured, and the Michigan Chapter met in Detroit for a special meeting at which Dr. Richard R. Trail of London, Regent for the College in England, lectured.

We are happy to report the formation of the Arkansas Chapter this year, which was the result of the good work done by our Immediate Past-President, Dr. William A. Hudson, who organized the chapter in Little Rock on February 24 and presented a lecture at the chapter's first scientific session.

In the international picture, it is gratifying to note that 26 of our 35 chapters in countries outside the United States held scientific sessions during 1955 and a number of these chapters are also holding scientific meetings periodically through the year. The following report will give you a resume of the activities of these chapters:

CHAPTER	LOCATION	DATE	ATTENDANCE
BRAZIL			
Rio Grande Do Sul	Porto Alegre	June 23 (Inaugural Session)	30—Total
Pernambuco & Salvador	Recife (Joint Meeting)	June 25 & 26	Approximately 50
Finland	Helsinki	June	No attendance record
Greece	Athens	February	Well attended
North India	Amritsar	February 18	Good attendance
Israel	Ben Yaakov	April 28	Good attendance
North Italy	Rome	May 15	Approximately 50
South Italy	Naples	March 19	Approximately 50
Middle East	Beirut, Lebanon	Sept. 16-18	Large attendance
Philippines	Manila	February 10	66—Total
Portugal	Lisbon	December	Report not yet received
SPAIN			
Barcelona	Barcelona	June 11	Over 100
Madrid	Madrid	June 16-18	Over 100

A number of our chapters arranged special meetings, in addition to their regular sessions, for members of the College who were traveling. The Japanese Chapter particularly has held two outstanding meetings, one for Prof. Ludwig Heilmeyer, Governor for the College in Freiburg, Germany, who spoke in Tokyo before an audience of over 500 physicians. A second special meeting was held on September 19 in Tokyo when Dr. Chauncey Maher of Chicago spoke before a group of over 250 doctors. A meeting of the Hong Kong and China Chapter was arranged for Dr. Maher in Hong Kong on October 14th and we understand that there was a very large attendance. This chapter, organized on February 14, 1955, has held three scientific sessions in addition to the one for Dr. Maher and will meet again in December. Dr. Maher also spoke before a special session of the Hawaii Chapter in Honolulu on October 24.

Prior to speaking in Tokyo, Prof. Heilmeyer lectured before special meetings of the East India Chapter in Calcutta and the South India Chapter in Madras. Both of these meetings had large registrations.

Special meetings were arranged, in addition to their regular sessions, by the chapters in Peru, Chile, Argentina, Uruguay and Rio de Janeiro when Dr. Leon Unger of Chicago and Dr. Regina S. Greenebaum of Pittsburgh lectured.

The Mexican Chapter, which meets regularly, held a special meeting in January in Mexico City during the National Congress on Tuberculosis. Doctors Oscar Auerbach, J. Maxwell Chamberlain, Leo Eloesser and Irving Selikoff presented papers at this meeting and Dr. José Abello, our Governor for Madrid, also participated in the program.

The Northern and Southern Chapters in South Africa have held regular scientific sessions during the year, the Southern Chapter having its 66th meeting since its organization in 1948. A combined luncheon meeting was arranged by these two active chapters. In November, Dr. Corrin Hodgson of the Mayo Clinic spoke in Johannesburg at a special dinner meeting of the Northern Chapter and again in Cape Town before the Southern Chapter members and their guests at the University of Cape Town Hospital.

The Quebec Chapter has had two very successful sessions, one on February 25 when it met jointly with the Medical-Surgical Society and the Phtisiology

Society of Quebec in Montreal. The second meeting was held in conjunction with the Fourth Postgraduate Course sponsored by the chapter and the Provincial Committee for the Prevention of Tuberculosis. Dr. William A. Hudson presented the Edward Archibald Memorial Lecture at this session.

The Cuban Chapter has held several special meetings during the year in conjunction with other medical societies in that country at which time excellent scientific programs were presented.

One of the most important activities of the Committee on College Chapters was the organization of the College Speakers Bureau. Several hundred members of the College have enrolled in this Bureau and are available for speaking appointments. During the past year, many requests from College chapters for the services of the Speakers Bureau have been received. It is anticipated that during the next year more chapters will take advantage of this service.

Because of the increased interest in chapter programs and because we are already scheduling many meetings for 1956, there is every reason to believe that our chapters will continue to grow in importance and will proceed to develop their activities during the coming year.

Committee on College Chapters

Alvis E. Greer, Houston, Texas, Chairman

John B. Andosca, Boston, Mass.
Norman Arcese, Seattle, Wash.
Bert H. Cotton, Beverly Hills, Calif.
Harry Golembe, Liberty, N. Y.
Sydney Jacobs, New Orleans, La.
Nathan K. Jensen, Minneapolis, Minn.
Hollis E. Johnson, Nashville, Tenn.
Ray W. Kissane, Columbus, Ohio
Milton B. Kress, Baltimore, Md.
Alexander Libow, Miami Beach, Fla.
Joe H. Little, Mobile, Ala.
Arnold Minnig, Denver, Colo.
James L. Mudd, St. Louis, Mo.
Howell S. Randolph, Phoenix, Ariz.
Irving Willner, Newark, N. J.
Thomas B. Wiper, Belmont, Calif.

College Chapter News

SOUTHERN CHAPTER

At the annual meeting of the Southern Chapter, held at the Shamrock Hotel, Houston, Texas, November 13-14, the following officers were elected:

President:	Alfred Goldman, St. Louis, Missouri
1st Vice-President:	Robert E. Schwartz, Hattiesburg, Mississippi
2nd Vice-President:	Joe S. Cruise, Atlanta, Georgia
Secretary-Treasurer:	Daniel Jenkins, Houston, Texas

NEW ENGLAND STATES CHAPTER

A regular monthly meeting of the New England States Chapter was held in Boston, Massachusetts on November 16. Dr. William B. O'Brien, Wallum Lake, Rhode Island, was guest speaker and presented a lecture on "Collapse Therapy in the Drug Era."

Dr. Paul D. White, a Fellow of the College, addressed the New England States Chapter at a meeting held in the Joslin Auditorium of the Deaconess Hospital in Boston on December 21. Dr. White spoke on "The Management of Coronary Artery Disease."

PACIFIC NORTHWEST CHAPTER

The Pacific Northwest Chapters of the American College of Chest Physicians and the American Trudeau Society held their annual combined meeting on November 4 and 5 at the Willow Chest Centre, Vancouver, B. C.

Following the scientific sessions on November 4, the annual dinner was held at the Faculty Club of the University of British Columbia at which time Dr.

W. Elliott Harrison, Governor for the College in British Columbia, presented Dr. George S. Saxton, Vancouver, with a Certificate of Merit for his valued service as President of the Pacific Northwest Chapter of the College during 1952.

At the annual business meeting of the Chapter, the following officers were elected for 1956:

President:	Norman Arcese, Seattle, Washington
Vice-President:	Gordon L. Maurice, Portland, Oregon
Secretary:	Edward H. Morgan, Seattle, Washington

QUEBEC CHAPTER

The Quebec Chapter of the College met jointly with the Section on Diseases of the Chest of the Montreal Surgical Society, the Quebec Phthsiology Society and the Montreal Society of Phthsiology and Pneumonology on January 13, 1956, at the Bruchesi Institute in Montreal. Prof. Georges Canetti, Chief of Laboratories, Pasteur Institute, Paris, France, presented the Second Archibald-Dube-Rousseau Memorial Lecture and spoke on "Tuberculous Cavities—Bacteriologic, Anatomical and Clinical Points of View."

The officers of the chapter are the following:

President:	LaSalle Laberge, Sherbrooke, Quebec
1st Vice-President:	Gaetan Jarry, Montreal, Quebec
2nd Vice-President:	Jonathon F. Meakins, Montreal, Quebec
Secretary-Treasurer:	J. E. Labrecque, Quebec, Quebec

NEW JERSEY CHAPTER

The New Jersey Chapter of the College held a scientific session early in December at the Roosevelt Hospital for Diseases of the Chest in Metuchen, New Jersey. The program consisted of a conference dealing with the residual sterile tuberculous cavity. A dinner followed the meeting.

College News Notes

Dr. E. H. Robitzek, Staten Island, New York, **Dr. Irving J. Selikoff,** Paterson, New Jersey, Fellows of the College, and **Drs. Walsh McDermott** and **Karl Muschenheim,** New York City, were recipients of the Albert Lasker Award for contributions to the development of isoniazid. Hoffmann-LaRoche Laboratories, Nutley, New Jersey, and the Squibb Institute for Medical Research, New Brunswick, New Jersey, also participated in this group award. The awards were presented at the annual meeting of the American Public Health Association in Kansas City, Missouri, November 17, 1955.

Dr. Gustav A. Hedberg, Nopeming, Minnesota, Medical Director and Superintendent of the Nopeming Sanatorium, was awarded the Dearholt Medal at the meeting of the Mississippi Valley Tuberculosis Conference in Des Moines, Iowa, October 13-15, 1955.

Dr. Edward A. Piszczek, Executive Director of the Suburban Cook County Tuberculosis Sanitarium District, Hinsdale, Illinois, spoke on the public health aspects of immunology at the University of Buffalo School of Medicine, November 30.

Dr. Aldo A. Luisada, Chicago, Illinois, has been appointed associate editor of the journal *Angiology* and a member of the Professional Education Committee of the Chicago Heart Association.

Dr. H. J. Roberts, West Palm Beach, Florida, recently acted as special guest lecturer for the Section on General Practice of the Palm Beach County Medical Society.

Dr. Lionel Henry Opie of Rondebosch, South Africa, was recently announced as the 1956 Rhodes scholar for the Cape Province. He headed the successful medical students at the University of Cape Town and won a University scholarship and gold medal. Dr. Opie was one of the first prize winners of the 1954 Essay Contest of the American College of Chest Physicians. The prize money was used to attend the London Hospital Medical School as a visiting student from December 1954 to February, 1955.

COLLEGE ESSAY CONTEST

The 1956 Prize Essay Contest of the College is open to undergraduate medical students throughout the world. The Board of Regents has recommended that members of the College affiliated with medical schools be urged to bring the contest to the attention of the student body at their respective schools. Essays may be submitted on any phase of cardiac or pulmonary diseases. Three prizes will be awarded comprising certificates and cash awards in the amounts of $250, $100, and $50. The contest will close on April 10, 1956 and instructions for the preparation of manuscripts are as follows:

1) Five copies of the manuscript typewritten in English (double-spaced) should be submitted to the Committee on College Essay, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois, U. S. A.
2) The only means of identification of the author shall be a motto or other device on the title page and a sealed envelope bearing the same motto on the outside, enclosing the name and address of the author.
3) A letter from the Dean or Chairman of the Department of Medicine or Surgery of the medical school, certifying that the author is a medical student.

CARDIOVASCULAR RESEARCH AWARD

The Committee on Cardiovascular Diseases of the Council on Research, American College of Chest Physicians, offers an award of $500 for the best manuscript on "Acute Pulmonary Edema." The study may be of either an experimental or a clinical type and may include problems of therapy. The original work, based on personal research, should be presented before May 1, 1956. It may consist of an unpublished manuscript or a recently published article (after April 1, 1955). If the manuscript is unpublished, publication may take place either in *Diseases of the Chest*, or in another journal, according to the wish of the author.

For further information, please write to Dr. Aldo A. Luisada, Chairman, Section on Cardiovascular Physiology, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

HAWAII MEDICAL ASSOCIATION PLANNING CENTENNIAL CELEBRATION

The Hawaii Medical Association has extended an invitation to all members of the American College of Chest Physicians and their families to attend the celebration to commemorate their 100th Anniversary to be held in Honolulu, April 22 to 29, 1956.

An outstanding meeting has been planned in Honolulu next April which will include, in addition to the technical aspects, unusual and unique entertainment and hospitality. Opportunities will be made available to visit all the Islands in the territory where special festivities have been planned. All travel agencies and carriers serving the Territory of Hawaii have complete information on hand to help you in arranging your trip.

Note from the Editor

DISEASES OF THE CHEST is now read by physicians in 88 nations, a considerable number of whom do not read English. For some years, authors have been asked to prepare summaries including the salient points contained in their manuscripts. These summaries have appeared in English, French, and Spanish. Beginning with this issue, summaries will also appear in German. This became advisable because of the increase in readers of the journal in Austria, Germany, and Switzerland.

Authors who submit papers to be considered for publication in *DISEASES OF THE CHEST* are urgently requested to prepare short, concise summaries in one, two, three order to accompany their manuscripts. These summaries should be written so that from them alone the reader obtains the essence of the paper.

There are few parts of the world where one of the four languages in which our summaries appear is not read by physicians.

Jay Arthur Myers, M.D.

POSTGRADUATE COURSES

The next Laryngology and Bronchoesophagology Course, under the direction of Dr. Paul H. Holinger, Chicago, Illinois, will be given at the University of Illinois College of Medicine, March 5 through 17, 1956. Interested physicians are requested to write directly to the Department of Otolaryngology, University of Illinois, College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

The Department of Laryngology and Bronchoesophagology, Temple University Hospital and School of Medicine, has announced the following postgraduate courses to be presented during 1956, under the direction of Drs. Chevalier L. Jackson and Charles M. Norris: BRONCHOESOPHAGOLOGY: February 6-17; May 28-June 8; September 17-28; LARYNGOLOGY AND LARYNGEAL SURGERY: April 23-May 4; November 6-16. Tuition for each course is $250. Further information and applications may be obtained from Dr. Chevalier L. Jackson, 3401 North Broad Street, Philadelphia 40, Pennsylvania.

ANNOUNCEMENTS

V. Ray Bennett & Associates, Inc., of Los Angeles, developers of the original Intermittent Positive Pressure Breathing Oxygen Therapy Unit, have recently introduced three additional features on the Model TV-2P.

Supplementing the patented Bennett Flow-Sensitive Respiratory Valve, the new air/oxygen diluter, push-pull diluter control and Bennett/seal mouthpiece result in more efficient use of oxygen and increased comfort for patients. The new air/oxygen diluter permits dilution at 40%, 60% or 100% oxygen concentration as desired. The mixture is regulated with a simple movement of the new push-pull control. The Bennett/seal mouthpiece is virtually a smaller, more comfortable mask, easily adjustable by means of an elastic head band.

O.E.M. Corporation of East Norwalk, Connecticut, introduced a new Model 80T Cof-Flator. The Cof-Flator is the machine that coughs when the patient can't. It provides exsufflation with negative pressure to eliminate retained bronchial secretions in the treatment of atelectasis, poliomyelitis, bronchial asthma, respiratory failure, bronchiectasis and pulmonary emphysema. Six major improvements have been made in the new model: 1) New air filter; 2) separate expiratory and inspiratory circuits; 3) calibrated time control; 4) quieter operation; 5) reduced weight; and 6) improved pressure control.

MEDICAL SERVICE BUREAU

Positions Available

Assistant Medical Director wanted for 100 bed tuberculosis hospital; North American graduate, salary $8,500, complete maintenance. Apply: Medical Director & Superintendent, District Five Tuberculosis Hospital, London, Kentucky, or State Tuberculosis Hospital Commission, New State Office Building, Frankfort, Kentucky.

Medical Director wanted, North American graduate, five years tuberculosis experience, relatively new 100-bed tuberculosis hospital, salary $10,000, complete maintenance. Apply: State Tuberculosis Hospital Commission, New State Office Building, Frankfort, Kentucky.

Physicians specializing in tuberculosis and chest diseases wanted for 600-bed hospital, located 30 miles from Springfield, Missouri. Developing pediatrics department, in-service and affiliation program. Merit system benefits. Full maintenance and laundry minimum rate. Following positions are open: Physician I (tuberculosis) $6,000-$8,000; Physician II (tuberculosis) $8,000,-$11,000; Physician III (tuberculosis) $10,000-$13,000. Write: Medical Director, Missouri State Sanatorium, Mt. Vernon, Missouri.

CALENDAR OF EVENTS
NATIONAL AND INTERNATIONAL MEETINGS

22nd Annual Meeting, American College of Chest Physicians
Hotel Sherman, Chicago, Illinois, June 7-10, 1956

Fourth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Cologne, Germany, August 19-23, 1956

POSTGRADUATE COURSE

9th Annual Postgraduate Course on Diseases of the Chest
Bellevue-Stratford Hotel, Philadelphia, March 19-23, 1956

CHAPTER MEETING

Clinical Meeting, New York State Chapter
Park-Sheraton Hotel, New York City, February 17-18, 1956